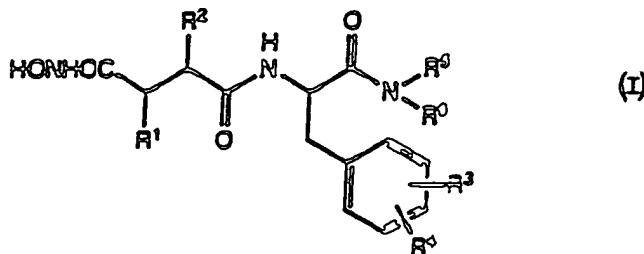




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(21) International Application Number: PCT/GB92/00230 (22) International Filing Date: 7 February 1992 (07.02.92) (30) Priority data: 9102635.1 7 February 1991 (07.02.91) GB (71) Applicant (for all designated States except US): BRITISH BIO-TECHNOLOGY LIMITED [GB/GB]; Watlington Road, Cowley, Oxford OX4 5LY (GB). (72) Inventors; and (75) Inventors/Applicants (for US only) : CRIMMIN, Michael, John [GB/GB]; 17 Cedar Drive, Marlow Bottom, Bucks SL7 3QB (GB). DAVIDSON, Alan, Hornsby [GB/GB]; 27 Newlands Mill, Witney, Oxon OX8 6HH (GB). BECKETT, Raymond, Paul [GB/GB]; 26 Saxel Close, Aston, Oxon OX8 2EB (GB).		(74) Agents: SHEARD, Andrew, Gregory et al.; Kilburn & Strode, 30 John Street, London WC1N 2DD (GB). (81) Designated States: AU, CA, FI, JP, KR, NO, US. Published <i>With international search report.</i>

(54) Title: HYDROXAMIC ACID DERIVATIVES, PROCESS FOR THEIR PREPARATION AND USE THEREOF

**(57) Abstract**

Compounds of general formula (I): wherein R^1 is hydrogen, C_1 - C_6 alkyl, phenyl, substituted phenyl, phenyl(C_1 - C_6 alkyl), or heterocyclyl; or R^1 is ASO_nR^7 wherein A represents a C_1 - C_6 hydrocarbon chain, optionally substituted with one or more C_1 - C_6 alkyl, phenyl or substituted phenyl groups $n = 0, 1, 2$; R^7 is C_1 - C_6 alkyl, phenyl, substituted phenyl, phenyl(C_1 - C_6 alkyl), heterocyclyl, (C_1 - C_6 alkyl)acyl thienyl or phenacyl; R^2 is hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, phenyl (C_1 - C_6 alkyl) or cycloalkyl(C_1 - C_6 alkyl); R^3 and R^4 are selected from hydrogen, halogen, cyano amino, amino(C_1 - C_6)alkyl, amino di (C_1 - C_6)alkyl, amino(C_1 - C_6)alkylacyl, aminophenacyl, amino (substituted phenacyl, amino acid or derivative thereof, hydroxy, oxy(C_1 - C_6)alkyl, oxyacyl, formyl, carboxylic acid, carboxamide, carboxy (C_1 - C_6) alkylamide, carboxyphenylamide, carboxy(C_1 - C_6) alkyl, hydroxy(C_1 - C_6)alkyl, (C_1 - C_6)alkyloxy(C_1 - C_6) alkyl or acyloxy(C_1 - C_6)alkyl, (C_1 - C_6)alkylcarboxylic acid, (C_1 - C_6) alkylcarboxy (C_1 - C_6) alkyl, amino (C_1 - C_6)alkylacyl carboxylic acid or amino (C_1 - C_6)alkylacyl (C_1 - C_6) alkylcarboxylate; or R^3 is OCH_2COR^8 R^4 is hydrogen; wherein R^8 is hydroxyl, C_1 - C_6 oxyalkyl, C_1 - C_6 oxyalkylphenyl, amino, C_1 - C_6 aminoalkyl, C_1 - C_6 aminodialkyl, C_1 - C_6 aminoalkylphenyl, an amino acid or derivative thereof; or R^3 is $OCH_2CH_2OR^9$ and R^4 is hydrogen; wherein R^6 is C_1 - C_6 alkyl, C_1 - C_6 alkylphenyl, phenyl, substituted phenyl, (C_1 - C_6 alkyl)acyl, or phenacyl; or R^3 is OCH_2CN and R^4 is hydrogen; R^5 is hydrogen or C_1 - C_6 alkyl, or (C_1 - C_6) alkylphenyl; R^6 is hydrogen or methyl; or a salt thereof; specifically excluded are compounds wherein: $R^3 = R^4 =$ hydrogen or $R^3 = R^4 =$ hydroxy or $R^3 =$ hydrogen and $R^4 =$ oxybenzyl or $R^3 =$ hydrogen and $R^4 =$ oxy(C_1 - C_6 alkyl); or a salt thereof; have collagenase inhibition activity and are useful in the management of disease involving collagen degradation. Its uses include rheumatoid arthritis, corneal ulceration, osteoporosis, periodontitis, gingivitis and tumour invasion.

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Hydroxamic acid derivatives, process for their preparation and use thereof

1

2

3 A number of small peptide like compounds which
4 inhibit metalloproteinase have been described.
5 Perhaps the most notable of these are those relating
6 to the angiotensin converting enzyme (ACE) where such
7 agents act to blockade the conversion of the
8 decapeptide angiotensin I to angiotensin II, a
9 potent pressor substance. Compounds of this type
10 are described in EP-A-0012401.

11

12 Certain hydroxamic acids have been suggested as
13 collagenase inhibitor as in US-A-4 599 361,
14 WO-A-9005716 and WO-A-9005719. Other hydroxamic acids
15 have been prepared as ACE inhibitors, for example, in
16 US-A- 4,105,789, while still others have been
17 described as enkephalinase inhibitors as in
18 US-A-4,495,540.

19

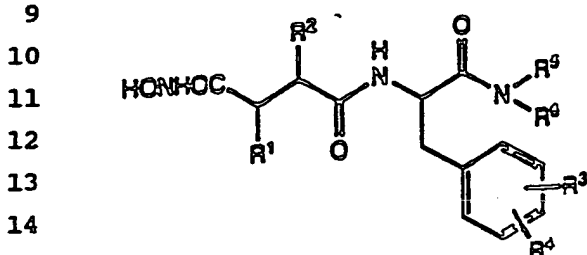
20 The hydroxamic acids of the current invention act
21 as inhibitors of mammalian collagenase which
22 initiates collagen breakdown. There is evidence
23 implicating collagenase as one of the key enzymes in
24 the breakdown of articular cartilage and bone in
25 rheumatoid arthritis (Arthritis and Rheumatism, 20,
26 1231-1239, (1977)). Potent inhibitors of collagenase
27 are useful in the treatment of rheumatoid arthritis
28 and related diseases in which collagenolytic activity
29 is important. These diseases include corneal
30 ulceration, osteoporosis, periodontitis, gingivitis
31 and tumour invasion.

32

33 The current invention relates to a series of hydroxamic

1 acids, which act as inhibitors of metalloproteinase,
2 their preparation, pharmaceutical compositions
3 containing them, and the intermediates involved in
4 their preparation.

6 In a first aspect of the invention there is provided a
7 compound of general formula I



I

16 Wherein :

18 R¹ is hydrogen, C₁ - C₆ alkyl, phenyl, substituted
19 phenyl, phenyl(C₁ - C₆ alkyl), or heterocyclyl;

21 or R^1 is $ASO_n R^7$

23 wherein A represents a C₁ - C₆ hydrocarbon chain,
24 optionally substituted with one or more C₁ - C₆ alkyl,
25 phenyl or substituted phenyl groups

27 $n = 0, 1, 2;$

29 R⁷ is C₁ - C₆ alkyl, phenyl, substituted phenyl, phenyl
30 (C₁-C₆ alkyl), heterocyclyl, (C₁ - C₆ alkyl)acyl,
31 thienyl or phenacyl;

33 R² is hydrogen, C₁ - C₆ alkyl, C₂ - C₆ alkenyl, phenyl
34 (C₁ - C₆alkyl) or cycloalkyl(C₁ - C₆ alkyl);

1
2 R^3 and R^4 are selected from hydrogen, halogen, cyano
3 amino, amino($C_1 - C_6$)alkyl, amino di($C_1 - C_6$)alkyl,
4 amino($C_1 - C_6$)alkylacyl, aminophenacyl, amino
5 (substituted) phenacyl, amino acid or derivative
6 thereof, hydroxy, oxy($C_1 - C_6$)alkyl, oxyacyl, formyl,
7 carboxylic acid, carboxamide, carboxy($C_1 - C_6$)
8 alkylamide, carboxyphenylamide, carboxy($C_1 - C_6$) alkyl,
9 hydroxy($C_1 - C_6$)alkyl, ($C_1 - C_6$)alkyloxy($C_1 - C_6$) alkyl
10 or acyloxy($C_1 - C_6$)alkyl, ($C_1 - C_6$)alkylcarboxylic
11 acid, ($C_1 - C_6$) alkylcarboxy($C_1 - C_6$) alkyl, amino
12 ($C_1 - C_6$)alkylacyl carboxylic acid or amino
13 ($C_1 - C_6$)alkylacyl ($C_1 - C_6$) alkylcarboxylate;
14
15 or R^3 is OCH_2COR^8 and R^4 is hydrogen;
16
17 wherein R^8 is hydroxyl, $C_1 - C_6$ oxyalkyl, $C_1 - C_6$
18 oxyalkylphenyl, amino, $C_1 - C_6$ aminoalkyl, $C_1 - C_6$
19 aminodialkyl, $C_1 - C_6$ aminoalkylphenyl, an amino acid
20 or derivative thereof;
21
22 or R^3 is $OCH_2CH_2OR^9$ and R^4 is hydrogen;
23
24 wherein R^9 is $C_1 - C_6$ alkyl, $C_1 - C_6$ alkylphenyl,
25 phenyl, substituted phenyl, ($C_1 - C_6$ alkyl)acyl, or
26 phenacyl;
27
28 or R^3 is OCH_2CN and R^4 is hydrogen;
29
30 R^5 is hydrogen or $C_1 - C_6$ alkyl, or ($C_1 - C_6$)
31 alkylphenyl;
32
33 R^6 is hydrogen or methyl;

1 or a salt thereof;

2

3 specifically excluded are compounds wherein:

4 $R^3 = R^4 = \text{hydrogen}$

5

6 or $R^3 = R^4 = \text{hydroxy}$

7

8 or $R^3 = \text{hydrogen}$ and $R^4 = \text{oxybenzyl}$

9 or $R^3 = \text{hydrogen}$ and $R^4 = \text{oxy}(C_1 - C_6 \text{ alkyl})$.

10

11 Hereafter in this specification the term "compound"
12 includes salt unless the context requires otherwise.

13

14 As used herein the term " $C_1 - C_6$ alkyl" refers to a
15 straight or branched chain alkyl moiety having from
16 one to six carbon atoms, including for example,
17 methyl, ethyl, propyl, isopropyl, butyl, t-butyl,
18 pentyl, hexyl and the like.

19

20 The term " $C_2 - C_6$ alkenyl" refers to a straight or
21 branched chain alkyl moiety having two to six carbons
22 and having in addition one double bond, of either E or
23 Z stereochemistry where applicable. This term would
24 include, for example, vinyl, 1-propenyl, 1- and
25 2-butenyl, 2-methyl-2-propenyl etc.

26

27 The term "cycloalkyl" refers to a saturated
28 alicyclic moiety having from 3 to 8 carbon atoms
29 and includes for example, cyclopropyl, cyclobutyl,
30 cyclopentyl, cyclohexyl and the like.

31

32 The term 'heterocyclyl' refers to a saturated or
33 unsaturated ring containing at least one hetero atom

1 such as nitrogen, oxygen or sulphur and includes for
2 example, furan, pyrrole, thiophene, morpholine,
3 pyridine, dioxane, imidazoline, pyrimidine and
4 pyridazine.

5
6 The term "substituted", as applied to a phenyl or other
7 aromatic ring, means substituted with up to four
8 substituents each of which independently may be C₁-C₆
9 alkyl, C₁-C₆ alkoxy, hydroxy, thiol, C₁-C₆ alkylthiol,
10 amino, halo (including fluoro, chloro, bromo and iodo),
11 trifluoromethyl, nitro, -COOH, -COONH₂ or -CONHR^A,
12 wherein R^A represents a C₁-C₆ alkyl group or the
13 characteristic side chain of an amino acid such as
14 alanine, valine, leucine, isoleucine, phenylalanine,
15 tryptophan, methionine, glycine, serine, threonine,
16 cysteine, tyrosine, asparagine, glutamine, aspartic
17 acid, glutamic acid, lysine, arginine or histidine.

18
19 The term "amino acid" means one of the following R or S
20 amino acids: glycine, alanine, valine, leucine,
21 isoleucine, phenylalanine, tyrosine, tryptophan,
22 serine, threonine, cysteine, methionine, asparagine,
23 glutamine, lysine, histidine, arginine, glutamic acid
24 and aspartic acid.

25
26 Derivatives of amino acids include acid halides, esters
27 and substituted or unsubstituted amides, for example N
28 methyl amide.

29
30 There are several chiral centres in the compounds
31 according to the invention because of the presence of
32 asymmetric carbon atoms.

33

1 The presence of several asymmetric carbon atoms gives
2 rise to a number of diastereomers with the appropriate
3 R or S stereochemistry at each chiral centre. The
4 invention is understood to include all such
5 diastereomers and mixtures thereof.

6
7 Preferred compounds include those in which,
8 independently or in combination :

9
10 R^1 represents a hydrogen atom or a $C_1 - C_4$ alkyl, or
11 phenyl group;

12
13 or R^1 represents ASO_nR^7 in which A is $C_1 - C_4$
14 hydrocarbon chain alkyl (for example methylene), $n =$
15 0, and R^7 is a phenyl, substituted phenyl or thienyl
16 group;

17
18 R^2 represents a $C_1 - C_5$ alkyl (for example isobutyl)
19 group;

20
21 R^3 represents cyano, aminoalkylacyl, amino
22 (C_{1-6})alkylacylcarboxylic acid, amino (C_{1-6})alkylacyl
23 (C_{1-6})alkylcarboxylate or OCH_2COR^8 and R^4 is hydrogen;

24
25 Wherein R^8 represents a hydroxyl group, $C_1 - C_6$
26 oxyalkyl, amino, $C_1 - C_6$ aminoalkylphenyl, $C_1 - C_6$
27 aminodialkyl, or an amino acid or derivative thereof;

28
29 R^5 represents a $C_1 - C_4$ alkyl (for example methyl)
30 group;

31
32 R^6 represents a hydrogen atom.

33

1 Particularly preferred compounds include:

2

3 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-
4 oxymethylcarboxylic acid)phenylalanine-N-methylamide;

5

6 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-
7 oxymethylcarboxy-N-methylamide)phenylalanine-N-
8 methylamide;

9

10 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-
11 oxymethylcarboxy-beta-alanine)phenylalanine-N-
12 methylamide;

13

14 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-
15 (oxymethylcarboxy-glycine)phenylalanine-N-methylamide;

16

17 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-
18 oxymethylcarboxy-N-benzylamide)phenylalanine-N-
19 methylamide;

20

21 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-cyano)
22 phenylalanine-N-methylamide;

23

24 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-
25 acetamido) phenylalanine-N-methylamide.

26

27 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxy-
28 methylcarboxamide)-phenylalanine-N-methylamide;

29

30 [4-(N-hydroxyamino)-2R-isobutyl-3S-(2-thienylthio
31 methyl succinyl)-L-(4-N-acetylamino)-phenylalanine-N-
32 methylamide;

33

- 1 [4-(N-hydroxyamino)-2R-isobutyl-3S-(2-thienylthio-
- 2 methylsuccinyl)]-L-(4-N-methylsuccinylamide)-phenyl-
- 3 alanine-N-methylamide;
- 4
- 5 [4-(N-hydroxyamino)-2R-isobutyl-3S-(4-aminophenylthio-
- 6 methyl)-succinyl]-L-(4-N-(methylsuccinylamide)-phenyl-
- 7 alanine-N-methylamide;
- 8
- 9 [4-(N-hydroxyamino)-2R-isobutyl-3S-(4-aminophenylthio-
- 10 methyl)-succinyl]-L-(4-N-(4-(4-oxobutanoic
- 11 acid)-aminophenylalanine-N-methylamide;
- 12
- 13 [4-(N-hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenyl-
- 14 thiomethyl)-succinyl]-L-(4-N-(methylsuccinylamido)-
- 15 phenylalanine-N-methylamide;
- 16
- 17 [4-(N(hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenyl-
- 18 thiomethyl)-succinyl]-L-(4-N-(4-(4-oxobutanoic
- 19 acid)-aminophenylalanine-N-methylamide;
- 20
- 21 [4-(N-hydroxyamino)-2R-isobutyl-3S-(2-thienylthio-
- 22 methyl)-succinyl]-L-4-(oxymethylcarboxymethyl)-phenyl-
- 23 alanine-N-methylamide.
- 24
- 25 [4-(N-hydroxyamino)-2R-isobutyl-3S-(2-thienylthio-
- 26 methyl)-succinyl]-L-(4-N-(oxymethylcarboxylic
- 27 acid)-phenylalanine-N-methylamide;
- 28
- 29 [4-(N-hydroxyamino)-2R-isobutyl-3S-(2-thienylthio-
- 30 methyl)-succinyl]-L-4-(oxymethylcarboxyglycyl methyl
- 31 ester)-phenylalanine-N-methylamide;
- 32
- 33 [4-(N-hydroxyamino)-2R-isobutyl-3S-(2-thienylthio-

1 methyl)-succinyl]-L-4-(oxymethylcarboxyglycine)-
2 phenylalanine-N-methylamide;

3

4 [4-(N-hydroxyamino)-2R-isobutyl-3S-methyl-succinyl]-L-
5 4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-
6 N-methylamide;

7

8 [4-(N-hydroxyamino)-2R-isobutyl-(3S-methyl-succinyl)-L-
9 4-(oxymethylcarboxyglycine)-phenylalanine-N-methyl-
10 amide;

11

12 [4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-4-(oxy-
13 methyl nitrile)-phenylalanine-N-methylamide;

14

15 [4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-3-(1-(2-
16 methoxycarbonyl)-ethyl)-4-methoxyphenylalanine-N-
17 methylamide;

18

19 [4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-3-(hydroxy-
20 methyl)-4-methoxyphenylalanine-N-methylamide; or

21

22 [4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-3-methyl-4-
23 methoxyphenylalanine-N-methylamide.

24

25 Compounds of the general formula I may be prepared by
26 any suitable method known in the art and/or by the
27 following process, which itself forms part of the
28 invention.

29

30 According to a second aspect of the invention, there is
31 provided a process for preparing a compound of general
32 formula I as defined above, the process comprising:

33

34 (a) deprotecting (for example by hydrogenation) a

1 compound of general formula II

2

3

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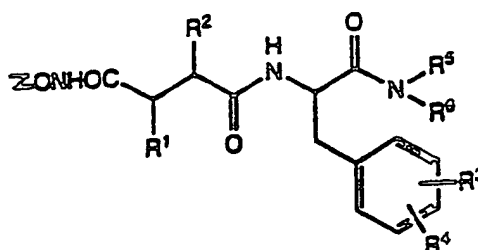
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9



II

10 Wherein:

11

12 R¹, R², R³, R⁴, R⁵ and R⁶ are as defined in the general
13 formula I and Z represents a suitable protective group
14 (e.g. tert-butyl, tertbutylsilyl, benzyl or substituted
15 benzyl);

16

17 (b) reacting a compound of general formula III

18

19

20

21

22

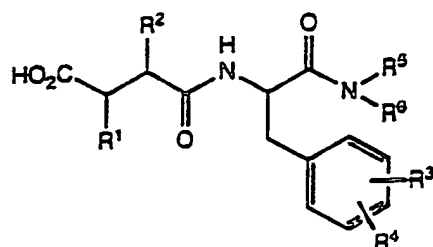
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25

26

27



III

28 Wherein:

29

30 R¹, R², R³, R⁴, R⁵, and R⁶ are as defined in the
31 general formula I,

32

33 with hydroxylamine or a salt thereof; and

1 (c) optionally after step (a) or step (b) converting a
2 compound of general formula I into another compound of
3 general formula I.

4

5 Compounds of general formula I which are sulfoxide or
6 sulphones can be derived from thio compounds of
7 general formula I by oxidation. Alternatively,
8 compounds of general formula II, or III which contain
9 sulphur can be oxidised.

10

11 A compound of general formula II can be obtained by
12 coupling, for example by conventional coupling
13 techniques, a compound of general formula III with
14 an O-protected hydroxylamine of formula NH_2OZ ; wherein
15 Z is as defined in general formula II.

16

17 A compound of general formula III can be prepared by

18

19 (a) de-esterifying (for example under acid or base
20 catalysis) a compound of general formula IV

21

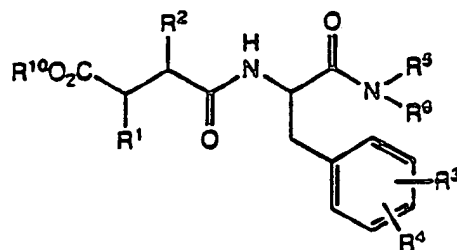
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IV

27 Wherein:

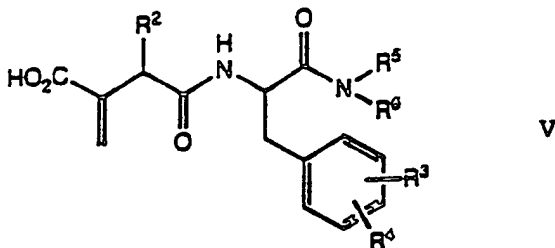
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29 R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are as defined in the
30 general formula I, and R^{10} represents a C_1 - C_6 alkyl or
31 benzyl group; or

32

33

1 (b) by reacting a compound of general formula V

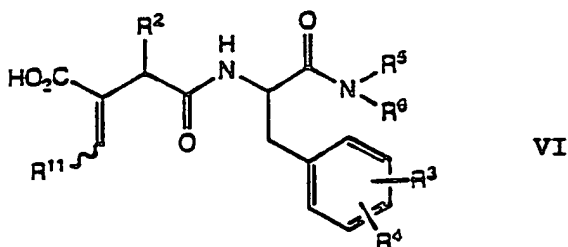


8 Wherein:

9
10 R^2 , R^3 , R^4 , R^5 , and R^6 are as defined in the general
11 formula I,

12
13 either with a thiol of general formula R^7SH , wherein
14 R^7 is as defined in general formula I, to give a
15 compound of general formula III in which R^1 is ASO_nR^7 ,
16 A represents a methylene group and n is 0.

17
18 or with compound R^1X where R^1 is benzyl or substituted
19 benzyl and X is F, Cl, Br or I in the presence of a
20 palladium catalyst to provide a compound of general
21 formula VI



28 Wherein:

29
30 R^2 , R^3 , R^4 , R^5 , and R^6 are as defined in the general
31 formula I, and R^1 is benzyl or substituted benzyl,
32 which may be converted to a compound of general
33 formula III wherein R^2 is benzyl or substituted benzyl,

1 by hydrogenation; or

2

3 (c) by converting a compound of general formula III
4 into another compound of general formula III.

5

6 A compound of general formula V can be prepared from
7 a compound of general formula IV

8

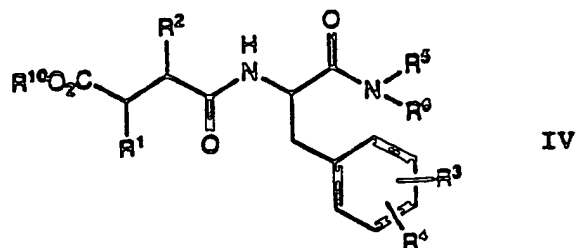
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13



14 Wherein:

15

16 R^2 , R^3 , R^4 , R^5 , and R^6 are as defined in the general
17 formula I, R^1 is carboxybenzyl or carboxy ($C_1 - C_6$)
18 alkyl and R^{10} is benzyl or ($C_1 - C_6$) alkyl, and R^{10} is
19 benzyl or ($C_1 - C_6$) alkyl,

20

21 by de-esterification (for example by hydrogenation)
22 followed by reaction with formaldehyde in the presence
23 of morpholine.

24

25 A compound of general formula IV can be prepared

26

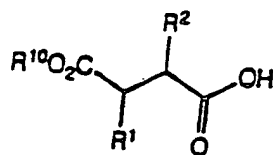
27 (a) By reacting, for example by conventional coupling
28 techniques, an acid of formula VII, or an activated
29 ester derivative thereof,

30

31

32

33

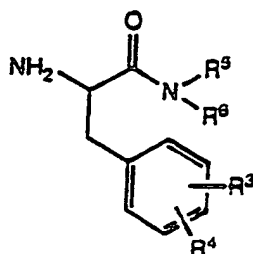


VII

Wherein:

R^1 and R^2 are as defined in the general formula I, and R^{10} is as defined above.

with an amine of general formula VIII



VIII

Wherein:

R^3 , R^4 , R^5 , and R^6 are as defined in the general formula I;

1 (b) by converting a compound of general formula IV into
2 another compound of general formula IV.

3

4 An amine of general formula VIII can be prepared by
5 deprotection (for example with trifluoroacetic acid)
6 of a compound of general formula IX

7

8

9

10

11

12

13

14

15

16 Wherein:

17

18

19 R^{12} is a conventional amine protecting group and R^3 ,
20 R^4 , R^5 and R^6 are as defined in general formula I.

21

22

23 A compound of general formula IX may be prepared by
24 coupling an acid of general formula X

25

26

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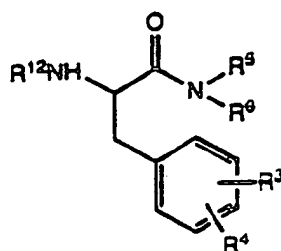
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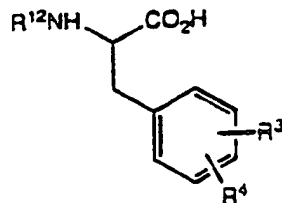
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32

33



IX



X

1 Wherein:

2

3 R^3 and R^4 , are defined as in general formula I, with
4 an amine of general formula XI

5

6

7



XI

8

9

10

11 Wherein:

12

13 R^5 and R^6 are as defined in general formula I

14

15 A compound of general formula X may be prepared

16

17 (a) by reaction of an aryl halide of general formula
18 XII

19

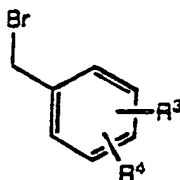
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XII

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26

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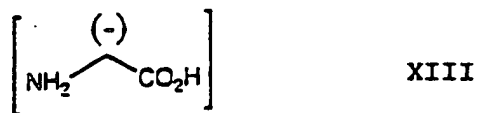
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29 Wherein R^3 and R^4 are as defined in general formula I
30 with a glycinate anion equivalent of formula XIII

31

32

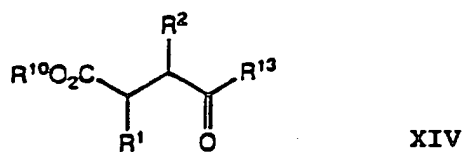
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followed by acid hydrolysis, protection of the amino function and base catalysed release of the carboxylic acid; or

(b) by converting a compound of general formula X to another compound of general formula X.

A compound of general formula VII may be prepared by reaction of a compound of general formula XIV



Wherein:

R^2 is as defined in the general formula I, R^1 is hydrogen, R^{10} is as described above and R^{13} is a chiral auxillary for example as described by Evans (J. Amer. Chem. Soc., 104, 1737, (1982)).

with lithium hydroxide/hydrogen peroxide.

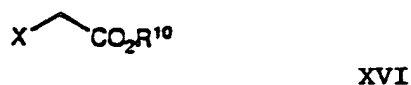
1 A compound of general formula XIV may be produced by
2 alkylation of the anion of a compound of general
3 formula XV



10 Wherein:

11
12 R² is as defined in the general formula I and R¹³ is a
13 chiral auxillary,

14
15 with an alkylating agent of general formula XVI.



21
22
23
24 Wherein:

25
26 R¹⁰ is as described above and X is a leaving group,
27 for example bromide, iodide or triflate.

28
29 Compounds of general formulae XI, XII, XIII, XV and XVI
30 and other reagents are either available commercially or
31 can be synthesised by simple chemical procedures.

32
33 The potency of compounds of the present invention to

1 act as inhibitors of collagenase was determined by
2 the procedure of Cawston and Barrett, (Anal. Biochem.,
3 99, 340 -345, 1979) whereby a 1mM solution of the
4 inhibitor being tested or dilutions thereof is
5 incubated at 37°C for 16 hours with collagen and
6 collagenase (buffered with Tris HCl - CaCl₂; pH
7 7.6). The collagen is acetylated ¹⁴C collagen
8 prepared by the method of Cawston and Murphy (Methods
9 in Enzymology, 80, 711, (1981)). The samples are
10 centrifuged to sediment undigested collagen and an
11 aliquot of the radioactive supernatant removed for
12 assay on scintillation counter as a measure of
13 hydrolysis. The collagenase activity in the presence
14 of 1 mM inhibitor, or a dilution thereof, is compared
15 to activity in a control devoid of inhibitor and the
16 results reported as that inhibitor concentration
17 effecting 50% inhibition of the collagenase.

18

19 In a further aspect of the invention there is provided
20 the use of a compound of general formula I in medicine,
21 particularly in a method of treatment of diseases in
22 which collagenolytic activity is important.

23

24 In another aspect of the invention there is provided
25 the use of a compound of general formula I in the
26 preparation of an agent for the treatment of diseases
27 in which collagenolytic activity is important.

28

29 The invention also provides a pharmaceutical
30 composition comprising one or more compounds of
31 general formula I in association with one or more
32 non-toxic pharmaceutically acceptable carriers and/or
33 diluents and/or adjuvants. Other active ingredients

1 may also be included in the compositions of the
2 invention.

3

4 The compositions of the present invention may be
5 formulated for administration by any route depending
6 on the disease being treated. The compositions may
7 be in the form of tablets, capsules, powders, granules,
8 lozenges, liquid or gel preparations, such as oral,
9 topical, or sterile parental solutions or
10 suspensions.

11

12 Tablets and capsules for oral administration may be in
13 unit dose presentation form, and may contain
14 conventional excipients. Examples of these are binding
15 agents such as syrup, acacia, gelatin, sorbitol,
16 tragacanth, and polyvinylpyrrolidone; fillers for
17 example lactose, sugar, maize-starch, calcium
18 phosphate, sorbitol or glycine; tableting lubricants,
19 for example magnesium stearate, talc, polyethylene
20 glycol or silica; disintegrants, for example potato
21 starch, or acceptable wetting agents such as sodium
22 lauryl sulphate. The tablets may be coated according
23 to methods well known in normal pharmaceutical
24 practice. Oral liquid preparations may be in the form
25 of, for example, aqueous or oily suspensions,
26 solutions, emulsions, syrups or elixirs, or may be
27 presented as a dry product for reconstitution with
28 water or other suitable vehicle before use. Such
29 liquid preparations may contain conventional additives
30 such as suspending agents, for example sorbitol,
31 syrup, methyl cellulose, glucose syrup, gelatin,
32 hydrogenated edible fats; emulsifying agents, for
33 example lecithin, sorbitan monooleate, or acacia;

1 non-aqueous vehicles (which may include edible
2 oils), for example almond oil, fractionated coconut
3 oil, oily esters such as glycerine, propylene glycol,
4 or ethyl alcohol; preservatives, for example methyl or
5 propyl p-hydroxybenzoate or sorbic acid, and if
6 desired conventional flavouring or colouring agents.

7

8 The dosage unit involved in oral administration may
9 contain from about 1 to 250 mg, preferably from about
10 25 to 250 mg. A suitable daily dose for a mammal may
11 vary widely depending on the condition of the
12 patient. However, a dose of about 0.1 to 300mg/kg body
13 weight, particularly from about 1 to 100 mg/kg body
14 weight may be appropriate.

15

16 For topical application to the skin the drug may be
17 made up into a cream, lotion or ointment. Cream or
18 ointment formulations that may be used for the drug
19 are conventional formulations well known in the art,
20 for example, as described in standard text books of
21 pharmaceutics such as the British Pharmacopoeia.

22

23 For topical applications to the eye, the drug may be
24 made up into a solution or suspension in a suitable
25 sterile aqueous or non-aqueous vehicle. Additives,
26 for instance buffers such as sodium metabisulphite or
27 disodium edeate; preservatives including bactericidal
28 and fungicidal agents, such as phenyl mercuric
29 acetate or nitrate, benzalkonium chloride or
30 chlorohexidine, and thickening agents such as
31 hypromellose may also be included.

32

33 The dosage employed for the topical administration

1 will, of course, depend on the size of the area being
2 treated. For the eyes each dose will be typically in
3 the range from 10 to 100 mg of the drug.

4
5 The active ingredient may also be administered
6 parenterally in a sterile medium. The drug
7 depending on the vehicle and concentration used, can
8 either be suspended or dissolved in the vehicle.
9 Advantageously, adjuvants such as local anaesthetic,
10 preservatives and buffering agents can be dissolved in
11 the vehicle.

12
13 For use in the treatment of rheumatoid arthritis the
14 compounds of this invention can be administered by
15 the oral route or by injection intra-articularly into
16 the affected joint. The daily dosage for a 70 kg
17 mammal will be in the range of 10 mgs to 1 gram.

18
19
20 The following examples illustrate the invention, but
21 are not intended to limit the scope in any way.

22
23
24 The following abbreviations have been used in the
25 Examples: DCM - Dichloromethane
26 DMF - N,N-Dimethylformamide
27 HOBT - Hydroxybenztriazole
28 NMM - N-Methylmorpholine
29 TFA - Trifluoroacetic acid
30 THF - Tetrahydrofuran
31 WSCDI - N-(Dimethylaminoethyl)-N'-ethylcarbodiimide.

32
33

EXAMPLESExample 1

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxylic acid)-phenylalanine-N-methylamide

Example 1a

N-(4-Methylpentanoyl)-4S-phenylmethyl-2-oxazolidinone

A dry 500 ml flask equipped with a magnetic stirrer was charged with (S)-4-Phenylmethyl-2-oxazolidinone (17.72g, 0.1 mol), this was capped with a rubber septum and flushed with N₂. Anhydrous THF (300 ml) was added via cannula and the resulting solution was cooled to -78°C in an acetone/dry ice bath. A solution of 1.47M n-butyllithium in hexane (68.4 ml, 0.101 mol) was transferred via cannula to a dry, septum-stoppered 100 ml dropping funnel. This was added dropwise to the THF solution over 10 minutes.

4-methyl valeric acid chloride (14.80g 0.11 mol) was added in one portion by syringe after completion of the addition of n-butyllithium. The resulting solution was stirred at -78°C for 30 minutes and then allowed to warm to ambient temperature over 30 minutes. Excess of the acid chloride was quenched by the addition of aq. NH₄Cl (60 ml) and the bulk of the solvent was removed. The resulting slurry was extracted with dichloromethane (2 x 80 ml). The combined organic extracts were washed with 1M NaOH (75 ml), brine (75 ml), dried (Na₂SO₄ anhyd.) and filtered. The solvent was removed to yield

1 a yellow oil (29.20g, 106%).

2

3 Analysis calculated for $C_{16}H_{21}NO_3$ Mwt = 275.34

4

5 δ_{H} (250 MHz, $CDCl_3$), 0.97 (6H, d, $C(CH_3)_2$, $J=6.2$
6 Hz), 1.53-1.76 (3H, m, CH_2CHMe_2), 2.78 (1H, dd, CH_2Ph ,
7 $J=9.5$ Hz), 2.85-3.05 (2H, m, $COCH_2$) 3.30 (1H, dd,
8 CH_2Ph , $J=3.3$ Hz) 4.16-4.25 (2H, m, CH_2OCO) 4.63-4.73
9 (1H, m, $CHBnz$) 7.19-7.34 (5H, m, C_6H_5)

10

11 Example 1b

12

13 N(4-(t-Butoxy)-2R-isobutylsuccinyl)-4S-phenylmethyl-2-
14 oxazolidinone

15

16 N-(4-Methylpentanoyl)-4S-phenylmethyl-2-oxazolidinone
17 (20g, 0.0726 mol) was placed in a dry 1 litre 3-necked
18 flask to which was added dry THF (400 ml). The mixture
19 was kept under a stream of Argon and cooled to -78°C
20 (dry ice/acetone). Sodium hexamethyldisilylamide (1M
21 solution in THF, 0.0726 mol, 72.6 ml) was added
22 dropwise through a dropping funnel (it was added to the
23 funnel via syringe). After stirring for 20 minutes,
24 t-butylbromoacetate (21.02g, 15.8 ml, 0.1089 mol, 1.5
25 equiv.) was added dropwise over 1 minute, to give an
26 orange solution. The mixture was kept at -78°C and
27 allowed to warm to -50°C over 2 hours (after which time
28 it turned pink). The reaction was then quenched by
29 adding acetic acid (10.90g, 10.4 ml, 0.1815 mol, 2.5
30 equiv.) in ether (50 ml) at -50°C whereupon the
31 solution became colourless. The solvent was removed
32 and the resulting slurry partitioned between ethyl
33 acetate and brine. The ethyl acetate layer was washed

1 once with brine and the original brine layer was
2 back-extracted with ethyl acetate. The combined
3 organic layers were dried and the solvent removed,
4 giving a yellow oil which crystallised on cooling
5 overnight to yield the title compound as a crystalline
6 solid (21.36g, 76%).

7

8 Analysis calculated for $C_{22}H_{31}O_5N$ MWt = 389.48

9

10 δ_H (250 MHz, $CDCl_3$) 0.91-0.96 (6H, dd, CMe_2 , $J=4.5$
11 Hz), 1.44 (9H, s, CMe_3) 1.24-1.72 (3H, m, CH_2CHMe_2),
12 2.49 (1H, dd, CH_2Ph , $J=4.6$ Hz), 2.72 (1H, dd,
13 $CH_2CO_2CH(CH_3)_3$, $J=2.3$ Hz), 3.36 (1H, dd, CH_2Ph , $J=3.25$
14 Hz), 4.16-4.18 (2H, m, CH_2OCO), 4.20-4.35 (1H, m,
15 $CH-CO$), 4.62-4.72 (1H, m, $CHBz$), 7.24-7.38 (5H, m,
16 C_6H_5)

17

18 $[\alpha]^{25}_D = + 66.9$ ($c=1$, MeOH)

19

20

21

22

23

24

25

26

27

28

29

30

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32

33

1 Example 1c

2

3 4-(t-Butoxy)-2R-isobutylsuccinic acid

4

5 N(4-(t-Butoxy)-2R-isobutylsuccinyl)-4S-phenylmethyl-2--
6 oxazolidinone (15.30g, 0.039 mol) was placed in a 1
7 litre flask with a stirrer bar and to it was added 750
8 ml of 4:1 THF:H₂O. This solution was stirred and cooled
9 to 0°C (ice/acetone bath) then 60% aq. H₂O₂ (4.5 ml,
10 0.157 mol, 4 equiv) was added via syringe over 5 mins,
11 followed by Li(OH)₂ (2.65g, 0.063 mol, 1.6 equiv.) in
12 100 ml water. The reaction mixture was stirred for 1h
13 at 0°C. TLC (10% methanol/dichloromethane) showed
14 complete reaction (product gave a yellow spot on TLC on
15 staining with bromocresol green and heating). The
16 reaction mixture was quenched with NaNO₂ (10.88g, 0.157
17 mol, 4 equiv.), the final pH was 12-13. THF was removed
18 in-vacuo and the aqueous layer extracted with
19 dichloromethane (3 x 200 ml) to recover the chiral
20 auxiliary. The organic extracts were dried (MgSO₄
21 anhyd.), solvent removed in-vacuo and the resulting
22 solid chiral auxiliary (7.05g, 0.039 mol, 100%)
23 recrystallised from ethyl acetate/hexane (2:1)

24

25

26 $[\alpha]_D^{25} = 13.0^\circ$ (x=1, MeOH)27 $[\alpha]_D^{25} = 4.9^\circ$ (c=1, EtOH)

28

29 The aqueous layer was cooled in an ice bath and
30 acidified to pH 5-6 with 2M HCl. The resulting cloudy
31 solution was extracted with ethyl acetate (4 x 200 ml),
32 readjusting the pH to 5-6 in between extractions. The
33 combined organic extracts were dried over MgSO₄,

1 filtered and the solvent was removed to yield the title
2 compound as a pale yellow oil (8.21g, 91%).

3

4 δ_{H} (250 MHz, CDCl_3) 0.93 (6H, dd, $J=7$, 8Hz), 1.28
5 (1H, m), 1.64 (1H, m), 2.38 (1H, dd, $J=16$, 5Hz), 2.59
6 (1H, dd, $J=16$, 9Hz), 2.85 (1H, m).

7

8 $[\alpha]_{\text{D}}^{25} = + 10.4$ ($c=1$, MeOH)

9

10 Example 1d

11

12 Pentafluorophenyl 4-(t-butoxy)-2R-isobutylsuccinate

13

14 A solution of the chiral acid (from example 1c, 5.0g,
15 21.7 mmol) and pentafluorophenol (8.0g, 43 mmol) in
16 dichloromethane (50 ml) was cooled to 0°C before
17 dropwise addition of N-methylmorpholine (2.7g, 26.7
18 mmol) followed by water-soluble carbodiimide (5.5g,
19 28.7 mmol) in several portions. After the WSCDI had
20 dissolved, a small amount of white insoluble material
21 remained which did not dissolve on addition of
22 N,N-dimethylformamide (5 ml). The mixture was allowed
23 to warm to room temperature and was then stirred
24 overnight at room temperature.

25

26 Solvents were removed on a rotary evaporator and the
27 residue was resuspended in dichloromethane (100 ml) and
28 washed successively with 1M HCl (2 x 200 ml), 0.5M
29 Na_2CO_3 (2 x 200 ml) and brine (200 ml) and dried
30 (Na_2SO_4). TLC (CH_2Cl_2) showed a single UV-active spot
31 (R_f ca. 0.8) with a small amount of brown baseline
32 impurity. The solution was therefore evaporated to a
33 brown oil and flushed through a silica column (2 x 20

1 cm) with dichloromethane. UV-positive fractions were
2 pooled and evaporated to give the pentafluorophenol
3 ester as a pale yellow oil (8.31g, 97%).

4
5 $C_{18}H_{21}F_5O_4$ Mwt = 396.35

6
7 i.r. (neat) 1785, 1732 cm^{-1}

8
9 δ_H (250 MHz, $CDCl_3$) 3.23 (1H, m), 2.74, 2.52 (2H,
10 ddd, J=9.3, 5.2, 16.8 Hz), 1.75 (2H, m), 1.46 (10H, s
11 and m), 0.98, 0.96 (6H, 2d, J=6.6 Hz)

12
13 δ_C (250 MHz, $CDCl_3$) 171.3, 170.3, 143.2-138.9,
14 81.4, 41.0, 39.5, 37.7, 28.0, 25.8, 22.6, 22.1

15
16 Example 1e

17
18 O-Benzyl-L-tyrosine N-methylamide

19
20 N-Boc-O-benzyl tyrosine methylamide (5.29g, 13.8 mmol)
21 was taken up in CH_2Cl_2 (100 ml). To the solution at 0°C
22 TFA (10 ml) was added dropwise and the solution allowed
23 to warm to ambient temperature. After 4 hours the
24 solvent and TFA were removed under vacuum. Any
25 remaining TFA was quenched with saturated $NaHCO_3$
26 solution (100 ml). The reaction mixture was extracted
27 using CH_2Cl_2 (100 ml) and washed with saturated $NaHCO_3$
28 solution (100 ml) and brine (100 ml). The CH_2Cl_2 layer
29 was dried over Na_2SO_4 and the solvent was removed under
30 vacuum to give a white solid, which was recrystallised
31 from ethyl acetate/hexane to yield the title compound
32 as a white crystalline solid (3.35g, 85.4%).

33

1 δ_{H} (250 MHz, CDCl_3) 7.45-7.33 (5H, bm, Bn-H), 7.23
2 (1H, bs, CONHMe), 7.13 (2H, d, $J=8.5$ Hz, Ar-H), 6.93
3 (2H, d, $J=8.6$ Hz, Ar-H), 5.06 (2H, s, CH_2), 3.56 (1H,
4 dd, $J=5.1, 4.0$ Hz, CH), 3.20 (1H, dd, $J=9.8, 4.0$ Hz, H
5 of CH_2), 2.82 (3H, d, $J=5.0$ Hz, NHCH_3), 2.65 (1H, dd,
6 $J=9.3, 4.5$ Hz, H of CH_2), 1.35 (2H, bs, NH_2).

7

8 Example 1f

9

10 [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-benzoyloxy)
11 phenylalanine-N-methylamide

12

13 To a stirred solution of the O-benzyl-L-tyrosine-N-
14 methylamide (from example 1e, 3g, 10.6 mmol) in DMF
15 (100 ml) was added the chiral pentafluorophenyl ester
16 (from example 1d, 8.37g, 21.1 mmol). The resulting
17 solution was stirred at room temperature overnight.
18 The DMF was removed under vacuum. The residue was
19 taken up in CH_2Cl_2 (200 ml) and washed with saturated
20 NaHCO_3 (2 x 100 ml), citric acid (2 x 100 ml) and brine
21 (100 ml). The organic layer was dried over MgSO_4 and
22 the solvent removed under vacuum to give a clear oil.
23 Flash chromatography (flash silica, CH_2Cl_2 to 5%
24 MeOH/ CH_2Cl_2) gave the title compound as a pale yellow
25 solid (4.95g, 94%).

26

27 $\text{C}_{29}\text{H}_{40}\text{N}_2\text{O}_5$ MWt = 496.65

28

29 δ_{H} (250 MHz, CDCl_3) 7.45-7.31 (5H, m, CH-21 to 25),
30 7.15 (2H, d, $J=8.6$ Hz, CH-9,11), 6.91 (2H, d, $J=8.6$ Hz,
31 CH-8,12), 6.30 (1H, d, $J=7.8$ Hz, CONH), 5.92 (1H, m,
32 CONHMe), 5.04 (2H, s, CH_2 -19), 4.50 (1H, q, $J=7.8$ Hz,
33 CH-5), 3.10 (1H, dd, $J=6.3, 6.2$ Hz, CH_2 -6a), 2.82 (1H,

1 dd, $J=7.8$ Hz, $\text{CH}_2\text{-6b}$), 2.70 (3H, d, $J=4.8$ Hz, $\text{CH}_3\text{-13}$),
2 2.61 (1H, m, CH-3), 2.46 (2H, m, $\text{CH}_2\text{-2a}$, 2b), 1.52 (2H,
3 m, 1.44, $\text{CH}_2\text{-15}$), (9H, s, $\text{CH}_3\text{-27}$, 28, 29), 1.19 (1H, m,
4 CH-16), 0.88, 0.85 (6H, 2d, $J=6.5$, 6.3 Hz, $\text{CH}_3\text{-17}$, 18).

5

6 Example 1g

7

8 [4-(*t*-Butoxy)-2*R*-isobutylsuccinyl]-L-(4-hydroxy)-
9 phenylalanine-N-methylamide

10

11 [4-(*t*-Butoxy)-2*R*-isobutylsuccinyl]-L-(4-benzyloxy)
12 phenylalanine-N-methylamide (2.19g, 4.4 mmol) was taken
13 up in 10% cyclohexene/ethanol (30 ml) and 10%
14 Pd/charcoal (0.219g) added. The mixture was then heated
15 under reflux. After 3 hours the hot solution was
16 filtered through glass fibre paper and the black solid
17 washed with methanol. The filtrate was concentrated
18 under reduced pressure to give the title compound as a
19 white foam (1.78g, 99%).

20

21 $\text{C}_{22}\text{H}_{34}\text{N}_2\text{O}_5$ MWt = 405.6

22

23 δ_{H} (250 MHz, CDCl_3) 7.08 (2H, d, $J=8.6$ Hz, CH-9,
24 11), 6.76 (2H, d, $J=8.6$ Hz, CH-8, 12), 6.35 (1H, d,
25 $J=8.0$ Hz, CONH), 5.91 (1H, m, CONHMe), 4.50 (1H, q,
26 $J=7.9$ Hz, CH-5), 3.06 (1H, dd, $J=6.2$ Hz, $\text{CH}_2\text{-6a}$), 2.96
27 (1H, dd, $J=7.9$ Hz, $\text{CH}_2\text{-6b}$), 2.71 (3H, d, $J=4.8$ Hz,
28 $\text{CH}_3\text{-13}$), 2.61 (1H, m, CH-3), 2.48 (2H, m, $\text{CH}_2\text{-2a}$, 2b),
29 1.52 (2H, m, $\text{CH}_2\text{-15}$), 1.44 (9H, s, $\text{CH}_3\text{-20}$, 21, 22),
30 1.25 (1H, m, CH-16), 0.86 (6H, d, $J=6.4$ Hz, $\text{CH}_3\text{-17}$,
31 18).

32

33 δ_{C} (250 MHz, CDCl_3) 173.8, 170.4, 154.2, 128.8,

1 126.3, 114.2, 79.8, 76.1-75.1, 53.7, 39.6, 36.7, 36.1,
2 26.6, 24.8, 24.2, 21.2, 20.9.

3

4 Example 1h

5

6 [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethyl-
7 carboxybenzyl)-phenylalanine-N-methylamide

8

9

10 [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-hydroxy)
11 phenylalanine-N-methylamide (2.69g, 6.6 mmol) was taken
12 up in dry acetone (150 ml). Anhydrous Na₂CO₃ (0.84g,
13 7.9 mmol) was added with stirring, followed by dropwise
14 addition of benzyl-2-bromoacetate (2.27g, 9.9 mmol).
15 The reaction flask was flushed with argon and then the
16 reaction mixture heated under reflux. After 48 hours
17 the solvent was removed under vacuum. The residue was
18 taken up in CH₂Cl₂ (100 ml) washed with saturated
19 Na₂CO₃ (100 ml), 1M HCl (100 ml) and brine (100 ml),
20 dried over MgSO₄ and the CH₂Cl₂ removed under vacuum to
21 give a yellow oil. Flash chromatography (flash silica,
22 2% MeOH/CH₂Cl₂) gave the title compound as a white
23 solid (1.91g, 52%).

24

25 C₃₁H₄₂N₂O₇ MWt = 554.69

26

27 δ_{H} (250 MHz, CDCl₃) 7.36 (5H, s, CH-23-27), 7.14
28 (2H, d, J=8.7 Hz, CH-9, 11), 6.83 (2H, d, J=8.7 Hz,
29 CH-8, 12), 6.33 (1H, d, J=7.9 Hz, CONH), 5.92 (1H, m,
30 CONHMe), 5.24 (2H, s, CH₂-21), 4.64 (2H, s, CH₂-19),
31 4.48 (1H, m, CH-5), 3.08 (1H, dd, J=6.2 Hz, CH₂-6a),
32 2.96 (1H, dd, J=7.9 Hz, CH₂-6b), 2.68 (3H, d, J=4.8 Hz,
33 CH₃-13), 2.63 (1H, m, CH-3, 2.46 (2H, m, CH₂-2a,2b),

1 1.48 (2H, m, CH₂-15), 1.43 (9H, s, CH₃-29, 30, 31),
2 0.87, 0.84 (6H, 2d, J=6.5 Hz, CH₃-17,18).

3

4 Example 1i

5

6 [4-Hydroxy-2R-isobutylsuccinyl]-L-(4-oxymethyl-
7 carboxybenzyl)-phenylalanine-N-methylamide

8

9 [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethyl-
10 carboxybenzyl)-phenylalanine-N-methylamide (2.12g, 3.8
11 mmol) was taken up in 95% TFA/H₂O (50 ml). The
12 solution was stirred at 0°C for 3 hours. TFA/H₂O
13 removed under vacuum. The residue was taken up in
14 CH₂Cl₂ (50 ml) washed with brine (3 x 50 ml) dried over
15 MgSO₄ and the solvent removed under vacuum to give the
16 title compound as a white solid (1.89g, 99%).

17

18 Example 1j

19

20 [4-(N-benzyloxyamino)-2R-isobutylsuccinyl]-L-(4-
21 oxymethylcarboxybenzyl)-phenylalanine-N-methylamide

22

23 [4-Hydroxy-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxy--
24 benzyl)-phenylalanine-N-methylamide (1.89g, 3.79 mmol)
25 was dissolved in CH₂Cl₂ (20 ml). To the solution was
26 added HOBT (0.63g, 4.17 mmol), WSCDI (1.09g, 5.6 mmol),
27 NMM (0.58g, 5.6 mmol) and after 15 minutes
28 benzylhydroxylamine (0.51g, 4.17 mmol). The reaction
29 mixture was stirred at room temperature. After 16
30 hours the solvent was removed. The yellow residue was
31 taken up in ethyl acetate whereupon white crystals
32 precipitated out, which were collected by filtration
33 and washed with ethyl acetate to yield the title

1 compound as a white solid (0.58g, 27%).

2

3 $C_{34}H_{41}N_3O_7$ Mwt = 603.72

4

5 δ_{H} (250 MHz, CDCl_3) 8.59, (1H, m, CONHOBz), 7.37
6 (10H, s, CH-23-27, CH-30 to 34), 7.11 (2H, d, $J=8.6$ Hz,
7 CH-9, 11), 6.80 (2H, d, $J=8.6$ Hz, CH-8,12), 6.47 (1H,
8 m, CONH), 5.95 (1H, m, CONHMe), 5.21 (2H, s, CH_2 -21),
9 4.87 (2H, m, CH_2 -28), 4.63 (2H, s, CH_2 -19), 4.52 (1H,
10 m, CH-5), 3.02 (2H, m, CH_2 -6a, 6b), 2.71 (3H, d+m,
11 $J=4.8$ Hz, CH_3 -13, CH-3), 2.42 (2H, m, CH_2 -2a, 2b), 1.46
12 (2H, m, CH_2 -15), 1.18 (1H, m, CH-16), 0.87, 0.84 (6H,
13 2d, $J=6.8$, 6.6 Hz, CH_3 -17,18).

14

15 Example 1k

16

17 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-
18 oxymethylcarboxylic acid)-phenylalanine-N-methylamide

19

20

21 [4-(N-benzyloxyamino)-2R-isobutylsuccinyl]-L-(4-
22 oxymethylcarboxybenzyl)-phenylalanine-N-methylamide
23 (467 mg, 0.77 mmol) was taken up in 10% cyclohexene/
24 ethanol (40 ml) and 20% Pd/charcoal (93 mg) added with
25 stirring. The solution was heated under reflux and
26 after 3 1/2 hours the solution filtered through glass
27 fibre paper. The filtrate was concentrated down under
28 reduced pressure to give the title compound as a white
29 solid (322 mg, 98%).

30

31 mpt = 168°C

32

33

1 Analysis calculated for $C_{20}H_{29}N_3O_7$ Mwt= 423.7

2

3 Requires C 56.73 H 6.90 N 9.92

4

5

6 Found C 56.52 H 6.91 N 9.59

7

8 δ_H (250 MHz, MeOD) 7.89 (1H, bd, CONHMe), 7.11 (2H,
9 d, J=8.4 Hz, CH-9,11), 6.81 (2H, d, J=8.4 Hz, CH-8,12),
10 4.56 (2H, s, CH₂-19), 4.44 (1H, m, CH-5), 3.05 (1H, dd,
11 J=6.4, 6.3 Hz, CH₂-6a), 2.87 (1H, dd, J=8.8, 9.0 Hz,
12 CH₂-6b), 2.64 (3H, s, CH₃-13), 2.78-2.58 (1H, bm, CH-3),
13 2.16 (1H, dd, J=4.7, 7.8 Hz, CH-2a), 2.04 (1H, dd,
14 J=6.5, 6.6 Hz, CH-2b), 1.36 (2H, m, CH₂-15), 1.13 (1H,
15 m, CH-16), 0.81, 0.77 (6H, 2d, J=6.3 Hz, CH₃-17, 18).

16

17 δ_C (250 MHz, DMSO) 173.34, 170.93, 169.80, 167.17,
18 155.8, 130.2, 129.5, 113.5, 64.1, 53.7, 40.4, 40.2,
19 40.0, 38.03, 35.86, 35.16, 25.10, 24.63, 22.78, 21.41.

20

21

22

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31

32

33

1 Example 2

2

3 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-
4 oxymethylcarboxy-N-methylamide)phenylalanine-N-
5 methylamide

6

7 Example 2a

8

9 [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxomethyl-
10 carboxylic acid)-phenylalanine-N-methylamide

11

12 Utilising the procedure described in example 1g but
13 employing [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-
14 (4-oxomethylcarboxybenzyl)-phenylalanine-N-methylamide
15 (from example 1h, 9.90 g, 17.85 mmol) in lieu of
16 [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-benzyloxy)-
17 phenylalanine-N-methylamide yielded, the title compound
18 as a white solid (8.07 g, 97.3%)

19

20 δ_{H} (250 MHz, CDCl_3) 7.07 (2H, d, $J=8.6$ Hz, CH-9,
21 11), 7.03 (1H, m, CONHCH), 6.79 (2H, d, $J=8.6$ Hz,
22 CH-8,12), 6.70 (1H, m, CONHMe), 4.63 (1H, m, CH-5),
23 4.60 (2H, s, CH₂-19), 2.96 (2H, d, $J=7.1$ Hz, CH₂-6),
24 2.66 (3H, d, $J=4.8$ Hz, CH₃-13), 2.65 (1H, s, CH-3),
25 2.65 (1H, s, CH-3), 2.43 (1H, dd, $J=8.5$ Hz, CH₂-2a),
26 2.33 (1H, dd, $J=5.3$ Hz, CH₂-2b), 1.45 (2H, m, CH₂-15),
27 1.41 (9H, s, CH₃-21,22,23), 1.20 (1H, m, CH-16), 0.82
28 (6H, dd, $J=6.3$, 6.2 Hz, CH₃-17,18).

29

30 δ_{C} (250 MHz, CDCl_3) 174.1, 170.7, 170.2, 155.3,

31

32 128.9, 128.4, 113.3, 79.6, 76.1-75.1, 63.7, 53.4, 39.8,
33 39.6, 36.7, 35.8, 26.6, 24.8, 24.2, 21.3, 20.8.

1

2 Example 2b

3

4 [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethyl-
5 carboxy-N-methylamide)-phenylalanine-N-methylamide

6

7 [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethyl-
8 carboxylic acid)-phenylalanine-N-methylamide (0.5g,
9 1.07 mmol) was dissolved in CH₂Cl₂ (100 ml). At 0°C
10 pentafluorophenol (0.4g, 2.15 mmol), WSCDI (0.26g, 1.3
11 mmol) and N-methylmorpholine (0.11g, 1.1 mmol) were
12 added. After 15 minutes 8M methylamine in ethanol
13 (0.25g, 2.7 mmol) was added dropwise. The solution was
14 allowed to warm to ambient temperature and stirred for
15 12 hours. A white solid of MeNH₂.HCl precipitated out,
16 but was not collected. The reaction solution was
17 washed with 1M HCl (100 ml), 1M Na₂CO₃ (100 ml) and
18 brine (100 ml). The CH₂Cl₂ layer was dried over MgSO₄
19 and the solvent removed under reduced pressure to give
20 the title compound as a white solid (0.44g, 86%).

21

22 δ_{H} (250 MHz, CDCl₃) 7.19 (2H, d, J=8.6 Hz, CH-9,
23 11), 6.84 (2H, d, J=8.6 Hz, CH-8,12), 6.60 (1H, m,
24 CONHMe), 6.27 (1H, d, J=7.8 Hz, CONH), 5.99 (1H, m,
25 CONHMe), 4.52 to 4.46 (3H, s+q, CH-5, CH₂-19), 3.09
26 (2H, m, CH₂-6a,6b), 2.92 (3H, d, J=4.8 Hz, CH₃-21),
27 2.72 (3H, d, J=4.8 Hz, CH₃-13), 2.61 (1H, m, CH-3),
28 2.46 (2H, m, CH₂-2a, 2b), 1.45 (11H, s+m, CH₃-23, 24,
29 25, CH₂-15) 1.20 (1H, m, CH-16), 0.87, 0.84 (6H, 2d,
30 J=6.3 Hz, CH₃-17,18).

31

32

33

1 Example 2c

2

3 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-
4 oxymethylcarboxy-N-methylamide)phenylalanine-N-
5 methylamide

6

7 The title compound was prepared from [4-(t-Butoxy)-
8 2R-isobutylsuccinyl]-L-(4-oxymethylcarboxy-N-
9 methylamide)-phenylalanine-N-methylamide utilising the
10 method described in examples 1i to 1k

11

12 mpt = 211°C

13

14 Analysis calculated for $C_{21}H_{32}N_4O_6$ Mwt = 436.51

15

16 Requires C 57.78 H 7.39 N 12.84

17

18 Found C 57.30 H 7.27 N 12.56

19

20 δ_{H} (250 MHz, DMSO) 10.39 (1H, s, CONH $\overline{\text{O}}$ H), 8.74 (1H,
21 s, CONH $\overline{\text{O}}$ H), 7.98 (2H, m, CONH $\overline{\text{H}}$ Me), 7.85 (1H, d, J=4.7
22 Hz, CONH $\overline{\text{H}}$), 7.12 (2H, d, J=8.5 Hz, CH-9,11), 6.83 (2H,
23 d, J=8.6 Hz, CH-8,12), 4.38 (2H, s, CH-19), 4.32 (1H,
24 m, CH-5), 2.96 (1H, dd, J=5.1, 5.0 Hz, CH₂-6a), 2.74
25 (1H, dd, J=9.6, 9.7 Hz, CH₂-6b), 2.64 (3H, d, J=4.7 Hz,
26 CH₃-21), 2.60 (1H, m, CH-3), 2.55 (3H, d, J=4.5 Hz,
27 CH₃-13), 2.05 (1H, dd, J=3.7, 7.0 Hz CH₂-2a), 1.91 (1H,
28 dd, J=7.5, 7.6 Hz, CH₂-2b), 1.28 (2H, m CH₂-15), 0.98
29 (1H, m, CH-16), 0.77, 0.72 (6H, 2d, J=6.3 Hz,
30 CH₃-17,18)

31

32 δ_{C} (250 MHz, DMSO) 173.3, 170.9, 167.6, 167.2,
33 155.7, 130.5, 129.6, 113.6, 66.7, 53.7, 40.4-36.0,

1 35.7, 35.2, 25.1, 24.9, 24.6, 22.8, 21.4

2

3

4 Example 3

5

6 4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl
7 carboxymethyl)-phenylalanine-N-methylamide

8

9 Example 3a

10

11 4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethyl
12 carboxymethyl)-phenylalanine-N-methylamide

13

14 [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethyl-
15 carboxylic acid) phenylalanine-N-methylamide (from
16 example 2a, 0.5g, 1.08 mmol) was dissolved in CH₂Cl₂
17 (20 ml) and cooled to 0°C. A solution of diazomethane
18 in ether (3 ml) was added via a pipette until gas
19 evolution ceased and the reaction solution remained a
20 pale yellow colour. After 30 minutes the reaction
21 mixture was treated with 10% acetic acid/ether until
22 the solution was colourless and washed with brine (30
23 ml). The CH₂Cl₂ layer was dried and the solvent
24 removed under reduced pressure to give the title
25 compound as a white solid (0.45g, 87%).

26

27 C₂₅H₃₃N₂O₇ Mwt = 478.69

28

29 delta_H (250 MHz, CDCl₃) 7.16 (2H, d, J=8.6 Hz, CH-9,
30 11), 6.83 (2H, d, J=8.6 Hz, CH-8,12), 6.35 (1H, d,
31 J=8.0 Hz, CONH), 5.91 (1H, m, CONHMe), 4.61 (2H, s,
32 CH₂-19), 4.49 (1H, q, J=7.9 Hz, CH-5), 3.61 (3H, s,
33 CH₃-21), 3.06 (1H, dd, J=6.2 Hz, CH₂-6a), 2.96, (1H,

1 dd, J=9.9 Hz, CH₂-6b), 2.71 (3H, d, J=4.8 Hz, CH₃-13),
2 2.59 (1H, m, CH-3), 2.48 (2H, m, CH₂-2a,2b), 1.53 (2H,
3 m, CH₂-15), 1.44 (9H, s, CH₃-23,24,25), 1.25 (1H, m,
4 CH-16), 0.86 (6H, 2d, J=6.4 Hz, CH₃-17,18).

5

6 Example 3b

7

8 4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl
9 carboxymethyl) phenylalanine-N-methylamide

10

11 The title compound was prepared from
12 4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethyl-
13 carboxymethyl) phenylalanine-N-methylamide utilising
14 the method described in examples 1i and 1k.

15

16 mpt = 187°C

17

18 Analysis calculated for C₂₁H₃₁N₃O₇ Mwt = 437.5

19

20 Requires C 57.65 H 7.14 N 9.60

21

22 Found C 57.63 H 7.11 N 9.27

23

24 δ_{H} (250 MHz, DMSO) 10.40 (1H, s, CONH₂OH), 8.76 (1H,
25 s, CONH₂OH), 7.99 (1H, d, J=8.0 Hz, CONH), 7.86 (1H, m,
26 CONHMe), 7.12 (2H, d, J=8.4 Hz, CH-9,11), 6.81 (2H, d,
27 J=8.4 Hz, CH-8,12), 4.73 (2H, s, CH₂-19), 4.33 (1H, m,
28 CH-5), 3.69 (3H, s, CH₃-21), 2.97 (1H, dd, J=4.6 Hz,
29 CH₂-6a), 2.76 (1H, dd, J=9.9, 10.1 Hz, CH₂-6b) 2.57,
30 3H, d, J=4.2 Hz, CH₃-13), 2.62-2.56 (1H, m, CH-3), 2.07
31 (1H, dd, J=6.9, 6.8 Hz, CH₂-2a), 1.93 (1H, dd, J=7.4,
32 7.6 Hz, CH₂-2b), 1.29 (2H, m, CH₂-15), 1.03 (1H, m,
33 CH-16), 0.78, 0.74 (6H, 2d, J=6.2 Hz, CH₃-17,18).

1
2 δ_C (250 MHz, DMSO) 173.3, 170.9, 166.6, 167.2,
3 155.6, 130.5, 129.6, 113.6, 64.2, 53.7, 51.3,
4 40.3-38.1, 35.8, 35.1, 25.1, 24.6, 22.7, 21.4

5

6

7 Example 4

8

9 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-
10 oxymethylcarboxy-N-benzylamide)-phenylalanine-N-methyl-
11 amide

12

13 Example 4a

14

15 [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-
16 oxymethylcarboxy-N-benzylamide)-phenylalanine-N-methyl-
17 amide.

18

19 Utilising the procedure described in example 2b
20 employing benzylamine (0.25g, 2.4 mmol) in lieu of
21 methylamine yielded the title compound as a white solid
22 (0.53g, 81%).

23

24 $C_{29}H_{41}N_3O_6$ MWt=527

25

26 δ_H (250 MHz, $CDCl_3$) 7.40-7.27 (5H, m, CH-23 to 27),
27 7.17 (2H, d, J=8.6 Hz, CH-9,11), 6.92 (1H, m, CONHBz),
28 6.85 (2H, d, J=8.6 Hz, CH-8,12), 6.29 (1H, d, J=7.8 Hz,
29 CONH), 5.96 (1H, m, CONHMe), 4.56-4.45 (5H, m, CH-5,
30 CH_2 -21, CH_2 -19), 3.04 (2H, m, CH_2 -6), 2.70 (3H, d,
31 J=4.8 Hz, CH_3 -13), 2.58 (1H, m, CH-3), 2.43 (1H, dd,
32 J=8.5 Hz, CH_2 -2a), 2.33 (1H, dd, J=5.3 Hz, CH_2 -2b),
33 1.45 (2H, m, CH_2 -15), 1.41 (9H, s, CH_3 -23,24,25), 1.20

1 (1H, m, CH-16), 0.86 (6H, 2d, J=6.3, 6.2 Hz,
2 CH₃-17,18).

3

4

5 Example 4b

6

7 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-
8 oxymethylcarboxy-N-benzylamide)-phenylalanine-N-methyl-
9 amide

10

11 The title compound was prepared from
12 [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethylene-
13 carboxy-N-benzylamide) phenylalanine-N-methylamide
14 utilising the method described in examples 1i to 1k.

15

16 mpt= 206°C

17

18 Analysis calculated for C₂₇H₃₆N₄O₆ MWt = 512.6

19

20 Requires C 63.26 H 7.08 N 10.93

21

22

23 Found C 62.52 H 7.09 N 10.97

24

25 delta_H (250 MHz, DMSO) 10.41 (1H, s, CONH₂OH), 8.76 (1H,
26 s, CONH₂OH), 8.62 (1H, t, J=6.1 Hz, CONHCHPh), 8.01 (1H,
27 d, J=8.3 Hz, CONH), 7.87 (1H, m, CONHMe), 7.26 (5H, m,
28 CH-23 to 27), 7.13 (2H, d, J=8.5 Hz, CH-9,11), 6.86
29 (2H, d, J=8.5 Hz, CH-8,12), 4.48 (2H, s, CH₂-19), 4.34
30 (2H, d, J=6.0 Hz, CH₂-21), 2.97 (1H, dd, J=4.5, 4.8 Hz,
31 CH₂-6a), 2.76 (1H, dd, J=9.5, 9.6 Hz, CH₂-6b),
32 2.64-2.55 (1H, bm, CH-3), 2.56 (3H, d, J=4.4 Hz,
33 CH₃-13) 2.06 (1H, dd, J=3.2, 7.1 Hz, CH₂-2a), 1.92 (1H,

1 dd, J=7.6 Hz, CH₂-2b), 1.28 (2H, m, CH₂-15), 0.97 (1H,
2 m, CH-16), 0.78, 0.73 (6H, 2d, J=6.3 Hz, CH₃-17,18).

3

4 delta_C (250 MHz, DMSO) 173.5, 170.9, 167.3, 167.2,
5 155.7, 138.6, 130.5, 129.6, 127.8, 126.8, 126.3, 113.9,
6 66.6, 53.7, 41.32, 40.1-38.1, 35.2, 25.1, 24.7, 22.8,
7 21.4

8

9

10 Example 5

11

12 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-
13 oxymethylcarboxy-beta-alanine)phenylalanine-N-
14 methylamide

15

16 Example 5a

17

18 [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxomethyl-
19 carboxy-beta-alanine benzyl ester) phenylalanine-N-
20 methylamide

21

22 Utilising the procedure described in example 2b
23 employing beta-alanine benzyl ester (0.76g, 2.16 mmol)
24 in lieu of methylamine yielded the title compound as a
25 yellow oil (0.65g, 97%).

26

27 C₃₄H₄₇N₃O₈ Mwt = 625

28

29 delta_H (250 MHz, CDCl₃) 7.35 (5H, s, CH-26 to 30), 7.17
30 (2H, d, J=8.5 Hz, CH-9,11), 7.19 (1H, m, CONHCH₂), 6.82
31 (2H, d, J=8.5 Hz, CH-8,12), 6.33 (1H, d, J=7.8 Hz,
32 CONH), 6.01 (1H, m, CONHMe), 5.13 (2H, s, CH₂-24), 4.49
33 (1H, q, J=6.7, 7.6 Hz, CH-5), 4.44 (2H, s, CH₂-19),

1 3.64 (2H, q, J=6.1 Hz, CH₂-21), 3.06 (2H, m, CH₂-6a,
2 6b), 2.72 (3H, d, J=4.8 Hz, CH₃-13), 2.66-2.62 (3H, m,
3 CH₂-22, CH-3), 2.50-2.39 (2H, m, CH₂2a,b), 1.48 (2H, m,
4 CH₂-15), 1.22, (1H, m, CH-16). 0.87, 0.84 (6H, 2d,
5 J=6.4, 6.3 Hz, CH₃-17, 18).

6

7 Example 5b

8

9 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-
10 oxymethylcarboxy-beta-alanine)phenylalanine-N-
11 methylamide

12

13 The title compound was prepared from [4-(t-butoxy)-
14 2R-isobutylsuccinyl]-L-(4-oxymethylcarboxy-beta-alanine
15 benzyl ester)phenyl alanine-N-methylamide utilising the
16 method described in examples 1i to 1k.

17

18 mpt = 195°C

19

20 Analysis calculated for C₂₃H₃₄N₄O₈ MWt = 494.6

21

22 Requires C 55.86 H 6.93 N 11.33

23

24 Found C 55.94 H 6.96 N 11.51

25

26 delta_H (250 MHz, MeOD) 7.13 (2H, d, J=8.5 Hz, CH-9,11),
27 6.86 (2H, d, J=8.5 Hz, CH-8,12), 4.47-4.42 (1H, m,
28 CH-5), 4.42 (2H, s, CH₂-19), 3.48 (2H, t, J=6.7 Hz,
29 CH₂-21), 3.06 (1H, dd, J=6.4, 6.3 Hz, CH₂-6a), 2.85
30 (1H, dd, J=8.7, 8.8 Hz, CH₂-6b), 2.80-2.64 (1H, m,
31 CH-3), 2.64 (3H, s, CH₃-13), 2.50 (2H, t, J=6.7 Hz,
32 CH₂-22), 2.17 (1H, dd, J=6.5 Hz, CH₂-2a), 2.04 (1H, dd,
33 J=6.5 Hz, CH₂-2b) 1.36 (2H, m, CH₂-15), 1.06 (1H, m,

1 CH-16), 0.81, 0.77 (6H, 2d, J=6.3 Hz, CH₃-17,18).

2

3 δ_{C} (250 MHz, MeOD) 177.0, 175.5, 173.9, 171.1,
4 170.6, 157.9, 132.0, 131.4, 115.8, 68.3, 56.2, 50.0,
5 49.6-47.9, 42.5, 42.4, 37.9, 36.8, 36.0, 34.6, 26.8,
6 26.3, 23.5, 22.

7

8

9 Example 6

10

11 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl
12 carboxy-glycine methyl ester) phenylalanine-N-
13 methylamide

14

15 Example 6a

16

17 [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-4-oxymethyl
18 carboxy-glycine methylester)-phenylalanine-N-
19 methylamide.

20

21 Utilising the procedure described in example 2b
22 employing glycine methyl ester hydrochloride (0.13g,
23 1.07 mmol) in lieu of methylamine yielded the title
24 compound as a white solid (0.45g, 78.5%).

25

26 C₂₇H₄₁N₃O₈ MWt = 535.64

27

28 δ_{H} (250 MHz, CDCl₃) 7.17 (2H, d, J=8.6 Hz,
29 CH-9,11), 7.15 (1H, m, CH₂CONHCH₂), 6.83 (2H, d, J=8.6
30 Hz, CH-8), 6.45 (1H, d, J=8.0 Hz, CHCONHCH), 6.26 (1H,
31 m, CONHMe), 4.53 (1H, m, CH-5), 4.48 (2H, s, CH₂-19),
32 4.13 (2H, d, J=6.3 Hz, CH₂-21), 3.76 (3H, s, CH₃-23),
33 3.04 (2H, m, CH₂-6), 2.72 (3H, d, J=4.8 Hz, CH₃-13),

1 2.51 (1H, m, CH-3), 2.42 (2H, m, CH₂-2), 1.47 (2H, m,
2 CH₂-15), 1.43 (9H, s, CH₃-24,25,26), 1.19 (1H, m,
3 CH-16), 0.83 (6H, dd, J=6.3 Hz, CH₃-17,18).

4

5 Example 6b

6

7 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl
8 carboxy-glycinemethylester)-phenylalanine-N-methylamide

9

10 The title compound was prepared from
11 [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-4-oxymethyl
12 carboxy-glycine methyl ester)-phenylalanine-N-
13 methylamide utilising the method described in examples
14 1i to 1k.

15

16 mpt = 180-185°C

17

18 Analysis calculated for C₂₃H₃₄N₄O₈ MWt = 494.55

19

20 Requires C 55.86 H 6.93 N 11.33

21

22 Found C 53.45 H 6.83 N 11.50

23

24 δ_{H} (250 MHz, MeOD) 7.14 (2H, d, J 8.6 Hz,
25 CH-9,11) 6.89, (2H, d, J=8.6 Hz, CH-8,12), 4.49 (2H, s,
26 CH₂-19), 4.44 (1H, m, CH-5), 3.99 (2H, s, CH₂-21), 3.69
27 (3H, s, CH₃-23), 3.11-2.81 (2H, m, CH₂-6), 2.72-2.63
28 (1H, m, CH-3), 2.64 (3H, s, CH₃-13), 2.21 (1H, dd, J=7.8
29 Hz, CH₂-2a), 2.04 (1H, dd, J=6.7, 6.6 Hz, CH₂-2b), 1.35
30 (2H, m, CH₂-15) 1.05 (1H, m, CH-16), 0.79 (6H, dd,
31 J=6.4 Hz, CH₃-17,18).

32

33 δ_{C} (250 MHz, MeOD) 177.1, 173.9, 171.8, 171.6,

1 170.6, 158.0, 132.1, 131.4, 115.9, 68.3, 56.3, 52.7,
2 50.0-48.0, 42.6, 42.4, 41.5, 37.9, 36.8, 26.8, 26.3,
3 22.3

4
5 Example 7

6
7 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl
8 carboxyethyl)-phenylalanine-N-methylamide.

9
10 Example 7a

11
12 [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethyl
13 carboxvethyl)-phenylalanine-N-methylamide.

14
15 When the procedure described in example 1g was utilised
16 employing [4-(t-butoxy)-2R-isobutylsuccinyl]-L-
17 (4-oxymethylcarboxybenzyl ester) phenylalanine-N-
18 methylamide (from example 1h 9.10g, 16.41 mmol) in lieu
19 of [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-benzyloxy)
20 phenylalanine-N-methylamide a transesterification
21 reaction occurred and an ethyl group was transferred
22 from the solvent to the reactant molecule. The
23 reaction yielded after chromatography (flash silica,
24 100% ethyl acetate) the title compound as a white solid
25 (0.51g, 6.3%)

26
27 $C_{26}H_{46}N_2O_7$ MWt = 492.62

28
29 1H nmr δ_{H} (250 MHz, $CDCl_3$) 7.09 (2H, d, J=8.6 Hz,
30 CH-9,11), 6.77 (2H, d, J=8.6 Hz, CH-8,12), 6.68 (1H, d,
31 J=8.8 Hz, CONHCH), 6.57 (1H, m, CONHMe), 4.55 (1H, m,
32 CH-5), 4.53 (2H, s, CH_2 -19), 4.21 (2H, q, J=7.1 Hz,
33 CH_2 -21), 2.97 (2H, m, CH_2 -6), 2.72-2.52 (1H, m, CH-3),

1 2.65 (3H, d, J=4.8 Hz, CH₃-13), 2.43 (1H, dd, J=7.8 Hz,
2 CH₂-2a), 2.27 (1H, dd, J=6.8 Hz, CH₂-2b), 1.42 (2H, m,
3 CH₂-15), 1.37 (9H, s, CH₃-23,24,25), 1.25 (3H, t, J=7.1
4 Hz, CH₃-22), 1.14 (1H, m, CH-16), 0.78 (6H, dd, J=6.4
5 Hz, CH₃-17,18).

6
7 Example 7b

8
9 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl
10 carboxyethyl)-phenylalanine-N-methylamide.

11
12 The title compound was prepared from
13 [4-(t-butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethyl-
14 carboxyethyl)-phenylalanine-N-methylamide utilising the
15 method described in examples 1i to 1k.

16
17 mpt 185°C

18
19 Analysis calculated for C₂₂H₃₃N₃O₇ MWt = 451.52

20
21 Requires C 58.52 H 7.37 N 9.31

22
23 Found C 58.54 H 7.28 N 9.26

24
25 δ_{H} (250 MHz, MeOD) 7.11 (2H, d, J=8.6 Hz, CH-9,11),
26 6.79 (2H, d, J=8.6 Hz, CH-8,12), 4.61 (2H, s, CH₂-19),
27 4.43 (1H, m, CH-5), 4.19 (2H, q, J=7.1, 7.2 Hz, CH₂-21),
28 3.05 (1H, dd, J=6.4, 6.4 Hz, CH₂-6a), 2.81 (1H, dd,
29 J=9.1, 8.9 Hz, CH₂-6b), 2.64 (3H, s, CH₃-13), 2.78-2.58
30 (1H, m, CH-3), 2.12 (1H, dd, J=7.8, 7.9 Hz, CH₂-2a),
31 2.06 (1H, dd, J=6.7, 6.8 Hz, CH₂-2b), 1.31 (2H, m,
32 CH₂-15), 1.24 (3H, t, J=7.1 Hz, CH₃-22) 1.09 (1H, m,
33 CH-16), 0.79 (6H, dd, J=6.4 Hz, CH₃-17, 18).

1 δ_C (250 MHz, MeOD) 177.2, 174.0, 171.0, 170.6,
2 158.1, 131.8, 131.2, 115.6, 66.4, 62.4, 56.4,
3 50.1, -48.0, 42.6, 42.4, 38.1, 36.9, 26.8, 26.4, 23.6,
4 22.4, 14.

5

6 Example 8

7

8 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl
9 carboxyglycine)phenylalanine-N-methylamide

10

11 Example 8a

12

13 [4-(t-Butoxycarbonyl)-2R-isobutylsuccinyl]-L-(4-
14 oxymethylcarboxyglycine benzyl ester)-phenylalanine-N-
15 methylamide

16

17 Utilising the procedure described in example 2b
18 employing glycine benzyl ester hydrochloride (0.24g,
19 1.21 mmol) in lieu of methylamine yielded the title
20 compound as a white solid (0.55g, 89.5%).

21

22 $C_{33}H_{45}N_3O_8$ MWt = 611.74

23

24 δ_H (250 MHz, $CDCl_3$) 7.38 (5H, m, CH-24 to 29),
25 7.22-7.11 (1H, m, $CONHCH_2CO_2Bz$), 7.17 (2H, d, $J=7.76$
26 Hz, CH-9, 11), 6.84 (2H, d, $J=7.6$ Hz, CH-8, 12), 6.47
27 (1H, d, $J=8.1$ Hz, $CHCONHCH$), 6.24 (1H, m, $CONHMe$), 5.19
28 (2H, s, CH_2-23), 4.62-4.42 (1H, m, CH-5), 4.48 (2H,
29 s, CH_2-19), 4.16 (2H, d, $J=6.5$ Hz, CH_2-21), 3.05 (2H,
30 m, CH_2-6), 2.77-2.55 (1H, m, CH-3), 2.73 (3H, d, $J=4.2$
31 Hz, CH_3-13), 2.53 (1H, dd, $J=6.6$ Hz, CH_2-2a), 2.35 (1H,
32 dd, $J=5.3$ Hz, CH_2-2b), 1.55-1.37 (2H, m, CH_2-15), 1.45
33 (9H, s, $CH_3-30,31,32$), 1.22, (1H, m, CH-16), 0.97 (6H,

1 m, CH₃-17,18).

2

3 Example 8b

4

5 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl
6 carboxyglycine)phenylalanine-N-methylamide

7

8 The title compound was prepared from [4-(t-
9 butoxycarbonyl)-2R-isobutylsuccinyl]-L-(4-oxymethyl-
10 carboxyglycine benzyl ester)-phenylalanine-N-
11 methylamide utilising the method described in examples
12 1i to 1k.

13

14 mpt = 142.5°C

15

16 Analysis calculated for C₂₂H₃₂N₄O₈ MWt = 480.52

17

18 Requires C 54.99; H 6.71 N 11.66

19

20 Found C 54.19; H 6.87 N 10.96

21

22 δ_{H} (250 MHz, DMSO) 10.42 (1H, s, CONHOH), 8.32 (1H,
23 m, CONHCH₂CO₂H), 8.01 (1H, d, J=8.1 Hz, CHCONHCH), 7.87
24 (1H, m, CONHMe), 7.13 (2H, d, J=7.6Hz, CH-9,11), 6.87
25 (2H, d, J=7.3 Hz, CH-8,12), 4.46 (2H, s, CH₂-21), 4.33
26 (1H, m, CH-5), 3.80 (2H, d, J=5.5 Hz, CH₂-19), 2.96
27 (1H, dd, J=4.6, 4.5 Hz, CH₂-6a), 2.75 (1H, m, CH₂-6b),
28 2.56 (3H, s, CH₃-13), 2.68-2.43 (1H, m, CH-3), 2.05
29 (1H, dd, J=7.0, 6.6 Hz, CH₂-2a), 1.91 (1H, dd, J=5.3
30 Hz, CH₂-2b), 1.26 (2H, m, CH₂-15), 1.05 (1H, m, CH-16),
31 0.75 (6H, dd, J=5.7 Hz, CH₃-17,18).

32

33 δ_{C} (250 MHz, DMSO) 173.4, 170.9, 170.5, 167.6,

1 167.2, 155.6, 130.6, 129.6, 113.9, 66.5, 53.7, 40.3,
2 40.2, 39.7-38.4, 5.9, 35.2, 25.9, 25.1, 22.8, 21.4

3

4 Example 9

5

6 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl
7 carboxy-N,N-dimethylamide)-phenylalanine-N-methylamide

8

9 Example 9a

10

11 [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethyl
12 carboxy-N,N-dimethylamide)-phenylalanine-N-methylamide.

13

14 Utilising the procedure described in example 2b
15 employing dimethylamine hydrochloride (0.11g, 1.30
16 mmol) in lieu of methylamine yielded the title compound
17 as a white solid (0.49g, 92.3%).

18

19 $C_{26}H_{41}N_3O_6$ MWt = 491.63

20

21 δ_{H} (250 MHz, CDCl_3) 7.13 (2H, d, $J=8.5$ Hz,
22 CH-9,11), 6.85 (2H, d, $J=8.5$ Hz, CH-8,12), 6.42 (1H, d,
23 $J=8.0$ Hz, CHCONHCH), 6.19 (1H, m, CONHMe), 4.63 (2H, s,
24 CH_2 -19), 4.50 (1H, m, CH-5), 3.12-2.82 (2H, m, CH_2 -6),
25 3.07 (3H, s, CH_3 -21), 2.96 (3H, s, CH_3 -22), 2.68 (3H,
26 d, $J=4.5$ Hz, CH_3 -13), 2.62 (1H, m, CH-3), 2.52 (1H, dd,
27 $J=8.5$ Hz, CH_2 -2a), 2.33 (1H, dd, $J=4.5$ Hz, CH_2 -2b),
28 1.55-1.35 (2H, m, CH_2 -15), 1.42 (9H, s, CH_3 -23,24,25),
29 1.19 (1H, m, CH-16), 0.83 (6H, dd, $J=6.3$ Hz,
30 CH_3 -17,18).

31

32

33

1 Example 9b

2

3 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl
4 carboxy-N,N-dimethylamide)-phenylalanine-N-methylamide

5

6 The title compound was prepared from
7 [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethyl-
8 carboxy-N,N-dimethylamide)-phenylalanine-N-methylamide
9 utilising the method described in examples 1i to 1k.

10

11 mpt 197°C

12

13 Analysis calculated for C₂₂H₃₄N₄O₆ MWt = 450.54

14

15 Requires C 58.65 H 7.61 N 12.44

16

17 Found C 58.58 H 7.54 N 12.33

18

19 delta_H (150 MHz, DMSO) 0.42 (1H, s, CONH₂OH), 8.77 (1H,
20 s, CONH₂OH), 7.99 (1H, d, J=8.0 Hz, CHCONHCH), 7.87 (1H,
21 m, CONHMe), 7.09 (2H, d, J=8.5 Hz, CH-9,11), 6.78 (2H,
22 d, J=8.5 Hz, CH-8,12), 4.71 (2H, s, CH₂-19), 4.32 (1H,
23 m, CH-5), 2.98 (3H, s, CH₃-21), 2.94 (1H, m, CH₂-6a),
24 2.83 (3H, s, CH₃-22), 2.73 (1H, m, CH₂-6b), 2.55 (3H,
25 m, CH₃-13), 2.68-2.45 (1H, m, CH-3), 2.01 (1H, dd,
26 J=6.8 Hz, CH₂-2a), 1.91 (1H, dd, J=6.8 Hz, CH₂-2b),
27 1.28 (2H, m, CH₂-15), 0.99 (1H, m, CH-16), 0.74 (6H,
28 dd, J=6.3, 6.2 Hz, CH₃-17,18).

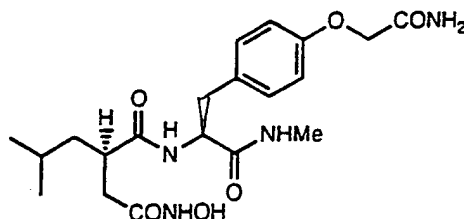
29

30 delta_C (250 MHz, CDCl₃) 173.4, 170.9, 167.2, 166.8,
31 156.1, 130.0, 129.4, 113.7, 65.5, 53.7, 40.9-38.0,
32 35.9, 35.2, 34.5, 25.1, 24.6, 21.4

33

Example 19

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxamide)-phenylalanine-N-methylamide (BB 802)



a) [4-t-Butoxy-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxamide)-phenylalanine-N-methylamide.

[4-t-Butoxy-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxylic acid)-phenylalanine-N-methylamide (see example 2a, 1.10g, 2.36 mmol) was dissolved in DMF (10ml) and cooled to 0°. Pentafluorophenol (0.87g, 4.72 mmol), aqueous ammonia (35%, 0.14g, 2.83 mmol), N-methyl morpholine (0.29g, 2.83 mmol) and WSCDI (0.54g, 2.83 mmol) were added and the reaction stirred overnight. The solvent was removed under high vacuum to leave a yellow oil which was dissolved in DCM and washed sequentially with saturated sodium carbonate, 2M hydrochloric acid and brine. The organic layer was dried over magnesium sulphate, filtered then the solvent removed to leave a white solid (0.89g, 1.92 mmol, 81%): $^1\text{H-NMR}$; δ (CDCl_3), 7.17 (2H, d, $J=8.6$ Hz, Aryl-H), 6.83 (2H, d, $J=8.6$ Hz, Aryl-H), 6.57 (2H, bs, CONH_2), 6.29 (1H, bq, NHMe), 6.17 (1H, bs, CONHCH), 4.57 (1H, q, $J=7.0$ Hz, COCHNH), 4.44 (2H, s, OCH_2CO), 3.04 (2H, d, $J=7.0$ Hz, CHCH_2Ar), 2.71 (3H, d, $J=4.8$ Hz, NHCH_3), 2.60 (1H, m, iBuCH), 2.50 (1H, dd, $J=14, 9$ Hz, CH_2CONHOH), 2.33 (1H, dd, $J=14, 5$ Hz, CH_2CONHOH), 1.43 (11H, m + s, $(\text{CH}_3)_2\text{CHCH}_2$ and $(\text{CH}_3)_3\text{CO}$), 1.17 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.86 (3H, d, $J=6.4$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.83 (3H, d, $J=6.3$ Hz, $\text{CH}(\text{CH}_3)_2$).

b) [4-(N-Benzylamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxamide)-phenylalanine-N-methylamide

[4-t-Butoxy-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxamide)-phenylalanine-N-methylamide (0.88g, 1.90 mmol) was taken up in

trifluoroacetic acid/water (95/5) and stored at 4° overnight. The trifluoroacetic acid was removed by evaporation and the residue taken up in DCM and washed with 2M sodium carbonate solution. The precipitated product was filtered off and dried to give the acid (0.57g, 1.40 mmol) as a white solid.

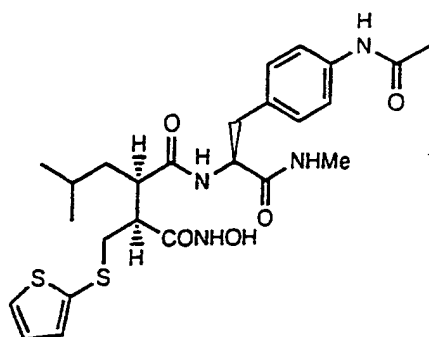
The acid from above (0.57g, 1.40 mmol) was dissolved in the minimum quantity of DMF. Pentafluorophenol (0.52g, 2.80 mmol), O-benzylhydroxylamine (0.34g, 2.80 mmol), N-methylmorpholine (0.18g, 1.82 mmol) and WSCDI (0.35g, 1.82 mmol) were added and the mixture stirred at room temperature overnight. The precipitated product was collected by filtration and washed with cold DCM, giving the title compound as a white solid (0.35g, 0.68 mmol, 49%): ¹H-NMR; δ (DMSO-d₆), 11.05 (1H, s, NH₂OH), 8.04 (1H, bd, J=8 Hz, CONHCH), 7.86 (1H, bm, NHMe), 7.5 - 7.3 (7H, s + m, CONH₂ + Ph), 7.12 (2H, d, J=8.6 Hz, Aryl-H), 6.82 (2H, d, J=8.6 Hz, Aryl-H), 4.75 (2H, s, OCH₂Ph), 4.33 (3H, bs, COCHNH and OCH₂CO), 2.93 (1H, dd, J=14, 5 Hz, CHCH₂Ar), 2.79 (1H, dd, J=14, 10 Hz, CHCH₂Ar), 2.60 (1H, m, iBuCH), 2.55 (3H, d, J=4.8 Hz, NHCH₃), 2.08 (1H, dd, J=14, 7 Hz, CH₂CONHOH), 1.94 (1H, dd, J=14, 7 Hz, CH₂CONHOH), 1.25 (2H, m, (CH₃)₂CHCH₂), 0.95 (1H, m, (CH₃)₂CHCH₂), 0.78 (3H, d, J=6.4 Hz, CH(CH₃)₂), and 0.73 (3H, d, J=6.3 Hz, CH(CH₃)₂).

c) [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxamide)-phenylalanine-N-methylamide.

[4-(N-Benzylamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxamide)-phenylalanine-N-methylamide (0.34g, 0.66 mmol) was dissolved in 10% cyclohexene/ethanol, 10% palladium on charcoal (40mg) added and the mixture heated at reflux for 1 hour. The reaction mixture was filtered hot then the solvents removed to leave the product as a white solid: m.p. 206.0 - 206.0°; ¹H-NMR; δ (Methanol-d₄), 7.13 (2H, J = 8.6 Hz, aryl-H), 6.86 (2H, d, J = 8.6 Hz, aryl-H), 4.51-4.38 (1H, m, NCHCO), 4.41 (2H, s, COCH₂CONH₂), 3.06 (1H, dd, J = 6.4 Hz, CHCH₂Ph), 2.84 (1H, dd, J=8.9 Hz, CHCH₂Ph), 2.71-2.57 (1H, m, iBuCH), 2.68 (3H, s, CONHCH₃), 2.14 (1H, dd, J=8, 10 Hz, CHCH₂CONHOH), 2.04 (1H, dd, J=6, 7 Hz, CHCH₂CONHOH), 1.36 (2H, m, (CH₃)₂CHCH₂CH), 1.07 (1H, m, (CH₃)₂CHCH₂CH), and 0.79 (6H, 2d, J = 6.4 Hz, CH(CH₃)₂); ¹³C NMR: δ (Methanol-d₄) 177.0, 174.1, 173.9, 170.6, 158.0, 132.0, 131.4, 115.7, 68.0, 57.1, 42.6, 42.4, 37.8, 36.8, 26.3, 25.7, 23.5 and 22.3.

Example 11

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-(4-N-acetylamino)-phenylalanine-N-methylamide (BB 887)



a) 4-Aminophenylalanine methyl ester.

4-Aminophenylalanine (20.0g, 96.4 mmol) was taken up in methanol (400 mL), cooled to -10° and thionyl chloride (100 mL) added dropwise maintaining the temperature of the reaction mixture below 0° . The solution was warmed to room temperature then refluxed for 24 hours. The solvent was removed to give a crude wax which was dissolved in ethyl acetate (500 mL) and washed with 1M sodium carbonate (100 mL). The aqueous layer was re-extracted with ethyl acetate (6 X 200 mL) and the combined organic layers dried over magnesium sulphate. Solvent removal gave the product as a pale yellow solid (16.6g, 85.2 mmol, 88%): $^1\text{H-NMR}$; δ (CDCl_3), 6.93 (2H, d, $J=8.3$ Hz, Aryl-H), 6.61 (2H, d, $J=8.3$ Hz, Aryl-H), 3.70 (3H, s, OCH_3), 3.66 (1H, dd, $J=5.2, 7.8$ Hz, NCHCO), 2.96 (1H, dd, $J=13.6, 5.2$ Hz, CH_2Ar), and 2.75 (1H, dd, $J=13.6, 7.7$ Hz, CH_2Ar).

b) 4-Aminophenylalanine-N-methylamide.

4-Aminophenylalanine methyl ester (16.5g, 85 mmol) was taken up in ethanol (200 mL) and stirred at 0° . Methylamine (100 mL, 8.03M in ethanol) was added dropwise and the mixture stirred at room temperature for four days. Solvent was removed at reduced pressure to leave the title compound as a yellow solid (16.4g, 100%): $^1\text{H-NMR}$; δ (CDCl_3), 7.24 (1H, bs, CONH), 6.95 (2H, d, $J=8.3$ Hz, Aryl-H), 6.60 (2H, d, $J=8.3$ Hz, Aryl-H), 3.49 (1H, dd, $J=4.1, 9.2$ Hz, NCHCO), 3.09 (1H, dd, $J=13.8, 4.1$ Hz, CH_2Ar), 2.77

(3H, d, $J=5.0$ Hz, NHCH_3), and 2.55 (1H, dd, $J=13.8, 9.2$ Hz, CH_2Ar).

c) [4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-L-4-aminophenylalanine-N-methylamide.

4-Aminophenylalanine-N-methylamide (4.92g, 25.5 mmol) was taken up in DMF (50 mL) and stirred at 0° , benzyl (2-benzyloxycarbonyl-5-methyl-3R-pentafluorophenoxycarbonyl)-hexanoate (11.10g, 28 mmol) was added and the mixture stirred at room temperature for six hours then overnight at 4° . The crude reaction mixture was taken up in diethyl ether then washed twice with 1M sodium carbonate, dried over magnesium sulphate. Solvent removal under vacuum left the crude product as a yellow foam which was purified from unreacted starting ester by column chromatography (silica gel, 0 - 3% methanol/DCM) to give the title compound as a foam (11.03g, 19.2 mmol, 76%) containing a mixture of diastereomers: $^1\text{H-NMR}$; δ (CDCl_3), 7.30 (10H, m, Ph), 6.98 (2H, d, $J=8.3$ Hz, Aryl-H), 6.59 (2H, d, $J=8, 3$ Hz, Aryl-H), 5.68 (1H, m, NHMe), 5.12 (4H, m, CH_2Ph), 4.42 (1H, m, NCHCO), 3.82 (1H, d, $J=9.3$ Hz, $\text{CH}(\text{CO}_2\text{Bn})_2$), 3.60 (1H, s, NH_2), 2.95 (3H, m, CH_2Ar and $^i\text{BuCH}$), 2.64 (3H, d, $J=5.0$ Hz, NHCH_3), 1.56 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 1.38 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 1.02 (1H, m, Me_2CHCH_2), and 0.78 (6H, m, $\text{CH}(\text{CH}_3)_2$).

d) [4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-L-4-(N-acetyl-amino)-phenylalanine-N-methylamide.

[4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-L-4-aminophenylalanine-N-methylamide (11.0g, 19.2 mmol) was dissolved in DCM and cooled to 0° then acetic anhydride (2.16g, 21.2 mmol), DMAP (50mg) and triethylamine (2.14g, 21.2 mmol) added. The reaction mixture was stirred for 2 hours then the reaction mixture diluted with an equivalent volume of DCM and washed twice with 2M hydrochloric acid then with brine and dried over magnesium sulphate. Filtration and solvent removal gave a pale yellow solid which was recrystallised from ethyl acetate/hexane (7.69g, 12.5 mmol, 65%): $^1\text{H-NMR}$; δ (CDCl_3), 7.59 (1H, s, ArNHCO), 7.42 (2H, d, $J=8.4$ Hz, Aryl-H), 7.30 (10H, m, Ph), 7.13 (2H, d, $J=8.4$ Hz, Aryl-H), 6.68 (1H, d, $J=7.9$ Hz, CHNHCO), 6.00 (1H, m, NHMe), 5.09 (4H, m, CH_2Ph), 4.50 (1H, m, NCHCO), 3.79 (1H, d, $J=9.3$ Hz, $\text{CH}(\text{CO}_2\text{Bn})_2$), 2.99 (3H, m, CH_2Ar and $^i\text{BuCH}$), 2.65 (3H, d, $J=5.0$ Hz, NHCH_3), 2.13 (3H, s, COCH_3), 1.55 (1H, m, Me_2CHCH_2), 1.35 (1H, m, Me_2CHCH_2), 1.06 (1H, m, Me_2CHCH_2), 0.77 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$ and 0.74 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$).

e) [Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-4-(N-acetylamino)-phenylalanine-N-methylamide.

[4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-L-4-(N-acetylamino)-phenylalanine-N-methylamide (7.69g, 12.5 mmol) was dissolved in ethanol (200 mL), 20% palladium on charcoal (1.5g) added and the mixture subjected to an atmosphere of hydrogen for 1 hour. The catalyst was removed by filtration and the solvent removed under vacuum to give the diacid as a foamy white solid (about 6g). This crude diacid was taken up in ethanol (250 mL), piperidine (1.17g, 13.7 mmol) and formaldehyde (37% aqueous solution, 9.4 mL, 125 mmol) were added and the reaction stirred at room temperature for three days. Solvent removal gave a clear oil which was taken up in ethyl acetate and washed twice with 1M hydrochloric acid and then with brine. The organic layer was separated and dried over magnesium sulphate then the solvent removed to give the title compound as a white solid (2.10g, 5.2 mmol, 42%): $^1\text{H-NMR}$; δ (Methanol- d_4), 7.81 (1H, s, ArNHCO), 7.39 (2H, d, $J=8.4$ Hz, Aryl-H), 7.07 (2H, d, $J=8.4$ Hz, Aryl-H), 6.19 (1H, s, $\text{H}_2\text{C}=\text{C}$), 5.59 (1H, s, $\text{H}_2\text{C}=\text{C}$), 4.47 (1H, m, NCHCO), 3.51 (1H, m, iBuCH), 2.99 (1H, dd, $J=13.8, 6.1$ Hz, CH_2Ar), 2.81 (1H, dd, $J=13.8, 8.7$ Hz, CH_2Ar), 2.64 (3H, s, NHCH_3), 2.06 (3H, s, COCH_3), 1.61 (1H, m, Me_2CHCH_2), 1.37 (1H, m, Me_2CHCH_2), 0.85 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.81 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$).

f) [4-Hydroxy-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-(4-N-acetylamino)-phenylalanine-N-methylamide.

[Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-4-(N-acetylamino)-phenylalanine-N-methylamide (1.63g, 4.04 mmol) was taken up in methanol (20 mL) and thiophene-2-thiol (5g) added then the mixture heated at reflux under argon overnight. The methanol was evaporated to give a crude yellow solid which was washed with cold diethyl ether to remove the bulk of the excess thiol. The title compound was then purified by crystallisation from ethyl acetate (1.61g, 3.1 mmol, 77%): $^1\text{H-NMR}$; δ (Methanol- d_4), 7.52 (2H, d, $J=8.4$ Hz, Aryl-H), 7.37 (1H, dd, $J=5.3, 1.2$ Hz, Thienyl-H5), 7.18 (2H, d, $J=8.4$ Hz, Aryl-H), 6.99 (1H, dd, $J=3.4, 1.0$ Hz, Thienyl-H3), 6.90 (1H, dd, $J=3.5, 5.3$ Hz, Thienyl-H4), 4.47 (1H, m, NCHCO), 3.51 (1H, m, iBuCH), 2.98 (1H, dd, $J=13.8, 5.2$ Hz, CH_2Ar), 2.78 (1H, dd, $J=13.7, 10.4$ Hz, CH_2Ar), 2.65 (3H, s, NHCH_3), 2.46 (3H, m, SCH_2CH), 2.06 (3H, s, COCH_3), 1.53 (1H, m, Me_2CHCH_2), 1.40 (1H, m, Me_2CHCH_2), 0.99 (1H, m, Me_2CHCH_2), 0.82 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.75 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$).

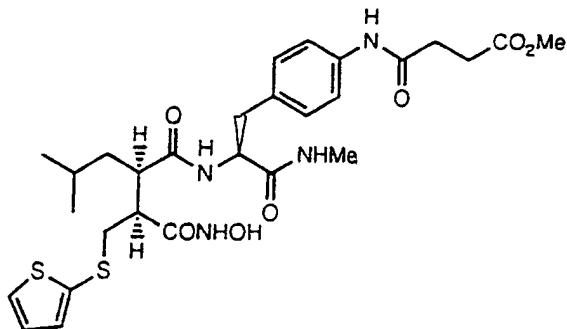
CH(CH₃)₂).

g) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-(4-N-acetylamino)-phenylalanine-N-methylamide.

[4-Hydroxy-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-(4-N-acetylamino)-phenylalanine-N-methylamide (1.08g, 2.08 mmol) was taken up in DMF (20 mL) and cooled to 0° while HOBT (0.36g, 2.70 mmol), NMM (0.27g, 2.70 mmol) and WSCDI (0.52g, 2.70 mmol) were added. The reaction was stirred at 0° for 3 hours then hydroxylamine hydrochloride (0.29g, 4.16 mmol) and NMM (0.42g, 4.20 mmol) were added and the reaction allowed to warm to room temperature overnight. The DMF was removed under reduced pressure and the resultant crude oil was taken up in diethyl ether/water (1:1) and the resulting solid collected by filtration. Impurities were removed by stirring the solid in boiling ethyl acetate to leave the title compound: ¹H-NMR ; δ (DMSO-d₆), 10.58 (1H, s, CONHOH), 9.84 (1H, s, CONHOH), 8.89 (1H, s, NHCOCH₃), 8.23 (1H, d, J=8.4 Hz, CONHCH), 7.80 (1H, m, CONHCHCH₃), 7.52 (1H, m, Thienyl-H), 7.50 (2H, m, Aryl-H), 7.15 (2H, d, J = 8.4 Hz, Aryl-H), 4.42 (1H, m, NHCHCCO), 3.02 (1H, m, COCHCH₂S), 2.90-2.62 (2H, m, CHCH2Ph), 2.54 (3H, d, J=4.7 Hz, CONHCH3), 2.40 (1H, m, iBuCH), 2.12 (2H, m, CHCH2S), 2.02 (3H, s, COCH3), 1.32 (2H, m, CH2CH(CH₃)₂), 0.83 (1H, m, CH2CH(CH₃)₂), and 0.78 (6H, 2xd, J = 6.3 Hz, CH(CH₃)₂): ¹³C NMR: δ (DMSO-d₆), 171.9, 170.9, 167.5, 167.4, 133.1, 132.2, 131.7, 128.9, 128.7, 127.2, 118.0, 54.1, 45.6, 45.5, 41.7, 40.1, 37.9, 35.8, 25.0, 24.6, 23.6 and 21.1.

Example 12

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-(4-N-(methyl succinylamido)-phenylalanine-N-methylamide (BB 1029)



a) [4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-L-4-(N-methylsuccinylamido)-phenylalanine-N-methylamide.

[4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-L-4-aminophenylalanine-N-methylamide (from example 11, 14.7g, 25.6 mmol) was dissolved in DCM and stirred at 0° while triethylamine (2.85g, 28.2 mmol), methyl succinyl chloride (4.24g, 28.2 mmol) and a catalytic amount of DMAP were added. The cooling bath was removed and the reaction stirred at room temperature for 2 hours. The reaction mixture was washed with 1M hydrochloric acid and saturated brine then dried over magnesium sulphate. Filtration and solvent removal gave the product as a cream solid (17.6g, 25.6 mmol, 100%): ¹H-NMR; δ (CDCl₃), 7.82 (1H, s, ArNHCO), 7.42 (2H, d, J=8.4 Hz, Aryl-H), 7.30 (10H, m, Ph), 7.13 (2H, d, J=8.4 Hz, Aryl-H), 6.66 (1H, d, J=7.8 Hz, CHNHCO), 5.89 (1H, d, J= 4.7 Hz, NHMe), 5.09 (4H, m, CH₂Ph), 4.47 (1H, dd, J+ 14.2, 7.7 Hz, NCHCO), 3.80 (1H, d, J=9.3 Hz, CH(CO₂Bn)₂), 3.69 (3H, s, CO₂CH₃), 2.92 (3H, m, CH₂Ar and BuCH), 2.71 (2H, d, J= 5.8 Hz, COCH₂CH₂), 2.65 (5H, m, NHCH₃ and CH₂CO₂Me), 1.55 (1H, m, (CH₃)₂CHCH₂), 1.33 (1H, m, (CH₃)₂CHCH₂), 1.02 (1H, m, Me₂CHCH₂), 0.77 (3H, d, J=6 Hz, CH(CH₃)₂) and 0.74 (3H, d, J=6 Hz, CH(CH₃)₂).

b) [Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-4-(N-methyl succinyl amido)-phenylalanine-N-methylamide.

[4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-L-4-(N-methylsuccinylamido)-phenylalanine-N-methylamide (12.80g, 25.2 mmol) was taken up in ethanol (500 mL), 10% palladium on charcoal added (3.5g) and the mixture stirred under hydrogen for 2 1/2 hours. The catalyst was removed by filtration and the solvent evaporated to leave the crude malonic acid which was used without further purification. This crude diacid was taken up in ethanol (500 mL), piperidine (2.36g, 27.8 mmol) and formaldehyde (37% aqueous solution, 22.7 mL, 278 mmol) were added and the reaction stirred at room temperature for three days. Solvent removal gave a clear oil which was taken up in ethyl acetate and washed twice with 1M hydrochloric acid and then with brine. The organic layer was separated and dried over magnesium sulphate then the solvent removed to give the title compound as a white solid which was purified by recrystallisation from ethyl acetate (5.96g, 12.5 mmol, 50%): ¹H-NMR; δ (Methanol-d₄), 7.81 (1H, s, ArNHCO), 7.39 (2H, d, J=8.3 Hz, Aryl-H), 7.06

(2H, d, $J=8.4$ Hz, Aryl-H), 6.19 (1H, s, $\text{H}_2\text{C}=\text{C}$), 5.59 (1H, s, $\text{H}_2\text{C}=\text{C}$), 4.48 (1H, m, NCHCO), 3.51 (1H, m, iBuCH), 2.98 (1H, dd, $J=13.7, 6.1$ Hz, CH_2Ar), 2.80 (1H, dd, $J=13.8, 8.7$ Hz, CH_2Ar), 2.63 (7H, bs, NHCH_3 and $\text{CH}_2\text{CH}_2\text{CO}_2\text{Me}$), 1.59 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 1.38 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.85 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.81 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$).

c) [4-Hydroxy-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-4-(N-methylsuccinylamido)-phenylalanine-N-methylamide.

[Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-4-(N-methylsuccinyl amido)-phenylalanine-N-methylamide (1.0g, 2.1 mmol) was taken up in methanol (20 mL) and thiophene-2-thiol (4g) added then the mixture stirred at reflux under argon overnight. Solvent removal gave a yellow solid which was washed twice with diethyl ether to leave the title compound as a white solid (0.96g, 1.62 mmol, 78%): $^1\text{H-NMR}$; δ (Methanol- d_4), 8.37 (1H, d, $J=8.5$, CONHCH), 7.83 (1H, $J=5.6$ Hz, NHMe), 7.51 (2H, d, $J=8.5$ Hz, Aryl-H), 7.37 (1H, dd, $J=5.3, 1.0$ Hz, Thienyl-H5), 7.17 (2H, d, $J=8.5$ Hz, Aryl-H), 6.99 (1H, dd, $J=3.6, 1.2$ Hz, Thienyl-H3), 6.90 (1H, dd, $J=3.5, 5.3$ Hz, Thienyl-H4), 4.53 (1H, m, NCHCO), 3.27 (3H, s, CO_2CH_3), 2.97 (1H, dd, $J=13.7, 5.3$ Hz, CH_2Ar), 2.77 (1H, dd, $J=13.7, 10.3$ Hz, CH_2Ar), 2.62 (7H, s, NHCH_3 and $\text{CH}_2\text{CH}_2\text{CO}_2\text{Me}$), 2.50 (3H, m, SCH_2CH), 2.06 (1H, s, iBuCH), 1.51 (1H, m, Me_2CHCH_2), 1.29 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.99 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.82 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.75 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$).

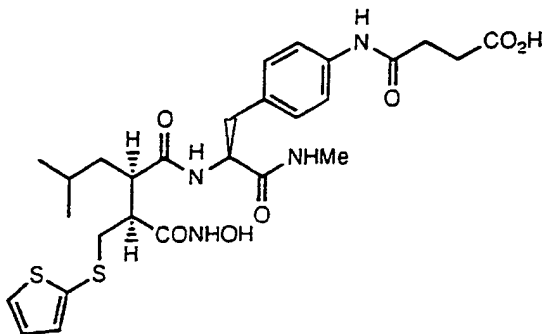
d) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-(4-N-(methyl succinylamido)-phenylalanine-N-methylamide.

[4-Hydroxy-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-4-(N-methylsuccinylamido)-phenylalanine-N-methylamide (0.95g, 1.61 mmol) was taken up in DMF (20 mL) and cooled to 0° while HOBT (0.28g, 2.09 mmol), NMM (0.21g, 2.10 mmol) and WSCDI (0.40g, 2.09 mmol) were added. The reaction was stirred at 0° for 3 hours then hydroxylamine hydrochloride (0.22g, 3.22 mmol) and NMM (0.33g, 3.22 mmol) were added and the reaction allowed to warm to room temperature overnight. The DMF was removed under reduced pressure and the resultant crude oil was taken up in diethyl ether/water (1:1) and the resulting solid collected by filtration. This crude solid was purified by recrystallisation from methanol to give the title compound (0.61g, 1.01 mmol, 62%): Anal. for $\text{C}_{28}\text{H}_{38}\text{N}_4\text{O}_7\text{S}_2 \cdot 0.6\text{H}_2\text{O}$: Requires: C 54.46, H 6.40, N 9.07: Found: C 54.51, H

6.20, N 9.87: $^1\text{H-NMR}$ data; δ (DMSO- d_6), 9.89 (1H, s, NHOH), 8.90 (1H, s, CONHOH), 8.23 (1H, d, CHCONHCH), 7.76 (1H, m, CONHCH_3), 7.50 (3H, m, Aryl-H and Thienyl-H5), 7.13 (2H, d, $J=8.2$ Hz, Aryl-H), 6.96 (2H, m, Thienyl-H3,4), 4.40 (1H, m, NHCHCO), 3.57 (3H, s, CO_2CH_3), 2.78 (2H, m, CHCH_2Ar), 2.52 (7H, m, $\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$ and CONHCH_3), 2.45 (2H, m, CHCH_2S and iBuCH), 2.14 (2H, m, CHCH_2S), 1.32 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.85 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.78 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.71 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$): $^{13}\text{C NMR}$: δ (DMSO- d_6), 172.3, 171.9, 170.8, 168.9, 167.5, 137.2, 133.1, 132.2, 131.8, 128.1, 128.7, 127.0, 118.1, 53.7, 50.8, 45.6, 45.5, 40.01-38.0, 36.5, 30.4, 28.1, 25.0, 24.6, 23.6 and 21.0.

Example 13

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-(4-N-(4-(4-oxobutanoic acid)-aminophenylalanine-N-methylamide (BB 1030).

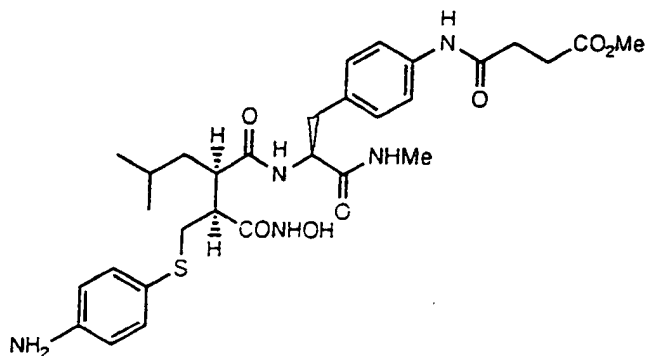


[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-(4-N-(methyl succinylamido)-phenylalanine-N-methylamide (147mg, 0.24 mmol) was suspended in methanol/water and lithium hydroxide (21 mg, 0.50 mmol) added. After six hours at room temperature the reaction was complete and the solution was neutralised with 1M hydrochloric acid. Removal of the solvents gave the title compound as a white solid (150 mg, 0.24 mmol, 100%): $^1\text{H-NMR}$; δ (DMSO- d_6), 10.63 (1H, s, NHOH), 10.17 (1H, s, CONHOH), 8.32 (1H, d, $J=8.3$ Hz, CONHCH), 7.87 (1H, m, CONHCH_3), 7.50 (3H, m, Aryl-H and Thienyl-H5), 7.13 (2H, d, $J=8.4$ Hz, Aryl-H), 6.96 (2H, m, Thienyl-H3,4), 4.40 (1H, m, NHCHCO), 2.77 (2H, m, CHCH_2Ar), 2.52 (7H, m, $\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$ and CONHCH_3), 2.46 (2H, m, CHCH_2S and iBuCH), 2.17 (2H, m, CHCH_2S), 1.32 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.83 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.81 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.73 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$): $^{13}\text{C NMR}$: δ (DMSO- d_6), 174.1, 171.9, 171.0, 169.9, 167.5, 137.4, 133.1, 132.3, 131.6, 129.0,

128.7, 127.2, 118.0, 54.8, 45.6, 45.5, 40.0, 38.4, 36.5, 31.6, 30.0, 25.0, 24.6, 23.6, and 21.0.

Example 14

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-aminophenylthiomethyl)-succinyl]-L-(4-N-(methyl succinylamido)-phenylalanine-N-methylamide (BB 1033)



a) [4-Hydroxy-2R-isobutyl-3S-(4-aminophenylthiomethyl)-succinyl]-L-4-(N-methylsuccinylamido)-phenylalanine-N-methylamide

[Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-4-(N-methylsuccinyl amido)-phenylalanine-N-methylamide (1.0g, 2.1 mmol) was treated with 4-aminothiophenol as described in example 12c to give the title compound (0.64g, 1.06 mmol, 51%): $^1\text{H-NMR}$; δ (Methanol- d_4), 7.49 (2H, d, $J=8.5$ Hz, Aryl-H), 7.17 (2H, d, $J=8.5$ Hz, Aryl-H), 6.96 (2H, d, $J=8.5$ Hz, Aryl-H), 6.54 (2H, d, $J=8.5$ Hz, Aryl-H), 4.54 (1H, dd, $J=10.1, 5.3$ Hz, NCHCO), 3.60 (3H, s, CO_2CH_3), 2.97 (1H, dd, $J=14.9, 5.2$ Hz, CH_2Ar), 2.80 (1H, bd, CH_2Ar), 2.63 (7H, s, NHCH_3 and $\text{CH}_2\text{CH}_2\text{CO}_2\text{Me}$), 2.42 (3H, m, SCH_2CH), 2.11 (1H, m, iBuCH), 1.49 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 1.28 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.97 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.82 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.75 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$).

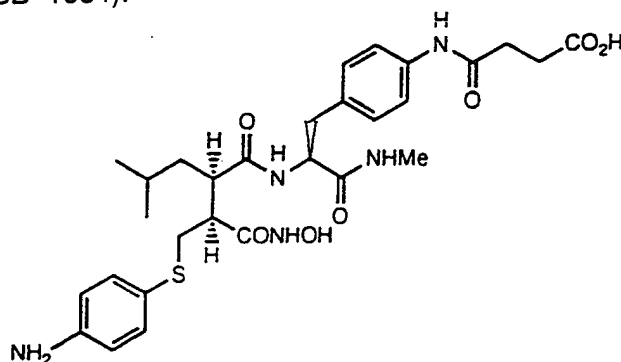
b) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-aminophenylthiomethyl)-succinyl]-L-(4-N-(methyl succinylamido)-phenylalanine-N-methylamide

[4-Hydroxy-2R-isobutyl-3S-(4-aminophenylthiomethyl)-succinyl]-L-4-(N-methylsuccinylamido)-phenylalanine-N-methylamide (0.61g, 1.02 mmol) was coupled with hydroxylamine as described in example 12d to produce the title compound which was recrystallised from ethyl acetate (0.42g,

0.68 mmol, 67%): $^1\text{H-NMR}$; δ (Methanol- d_4), 7.47 (1H, d, $J=8.4$ Hz, CONHCH), 7.13 (2H, d, $J=8.4$ Hz, Aryl-H), 6.88 (2H, d, $J=8.5$ Hz, Aryl-H), 6.56 (2H, d, $J=8.4$ Hz, Aryl-H), 4.58 (1H, m, NHCHCO), 3.60 (3H, s, CO_2CH_3), 2.99 (1H, m, CHCH_2Ar), 2.79 (1H, m, CHCH_2Ar), 2.66 (4H, m, $\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$), 2.56 (3H, s, CONHCH $_3$), 2.49 (2H, m, CHCH_2S and $i\text{BuCH}$), 2.10 (2H, m, CHCH_2S), 1.35 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.95 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.81 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.73 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$); $^{13}\text{C NMR}$: δ (Methanol- d_6), 175.5, 174.9, 173.9, 172.3, 171.5, 147.7, 138.9, 134.0, 133.7, 130.6, 123.6, 120.8, 117.1, 56.2, 50.0, 47.6, 41.5, 38.5, 36.4, 32.3, 30.0, 26.9, 26.2, 24.3 and 21.7.

Example 15

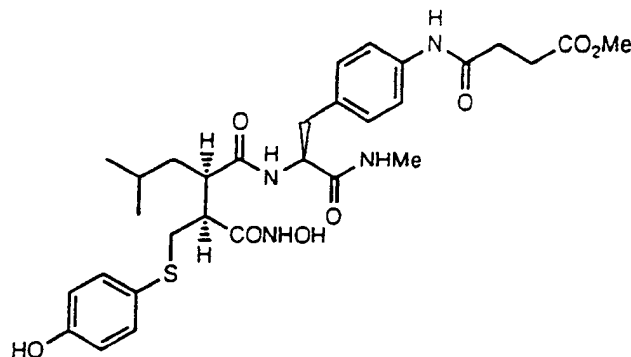
[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-aminophenylthiomethyl)-succinyl]-L-(4-N-(4-(4-oxobutanoic acid)-aminophenylalanine-N-methylamide (BB 1034).



[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-aminophenylthiomethyl)-succinyl]-L-(4-N-(methyl succinylamido)-phenylalanine-N-methylamide (142mg, 0.23mmol) was treated with lithium hydroxide as described in example 13 to give the title compound (140mg, 0.23 mmol, 100%): $^1\text{H-NMR}$; δ (DMSO- d_6), 10.89 (1H, s, NHOH), 10.54 (1H, s, NHOH), 9.02 (1H, bs, Aryl-NH), 8.31 (1H, d, $J=8.1$ Hz, CONHCH), 7.82 (1H, m, NHMe), 7.48 (2H, d, $J=8.1$ Hz, Aryl-H), 7.09 (2H, d, $J=8.4$ Hz, Aryl-H), 6.88 (2H, d, $J=8.3$ Hz, Aryl-H), 6.44 (2H, d, $J=8.4$ Hz, Aryl-H), 4.47 (1H, m, NHCHCO), 2.78 (2H, m, CHCH_2Ar), 2.51 (4H, m, $\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$), 2.41 (5H, s, CONHCH $_3$, CHCH_2S and $i\text{BuCH}$), 2.18 (2H, m, CHCH_2S), 1.32 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.83 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.77 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.73 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$); $^{13}\text{C NMR}$: δ (DMSO- d_6), 175.3, 172.2, 171.4, 171.0, 167.9, 147.8, 137.7, 133.1, 131.5, 126.8, 118.9, 117.9, 113.9, 53.9, 45.88, 45.6, 39.7-38.4, 37.1, 33.9, 33.3, 25.0, 24.6, 23.7 and 21.0.

Example 16

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenylthiomethyl)-succinyl]-L-(4-N-(methyl succinylamido)-phenylalanine-N-methylamide (BB 1035)



a) [4-Hydroxy-2R-isobutyl-3S-(4-hydroxyphenylthiomethyl)-succinyl]-L-4-(N-methylsuccinylamido)-phenylalanine-N-methylamide

[Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-4-(N-methylsuccinyl amido)-phenylalanine-N-methylamide (1.0g, 2.1 mmol) was treated with 4-hydroxythiophenol as described in example 12c to give the title compound (0.95g, 1.58 mmol, 75%): $^1\text{H-NMR}$; δ (Methanol- d_4), 7.51 (2H, d, $J=8.5$ Hz, Aryl-H), 7.20 (2H, d, $J=8.5$ Hz, Aryl-H), 7.02 (2H, d, $J=8.5$ Hz, Aryl-H), 6.63 (2H, d, $J=8.5$ Hz, Aryl-H), 4.58 (1H, dd, $J=10.1, 5.3$ Hz, NCHCO), 3.60 (3H, s, CO_2CH_3), 2.97 (1H, dd, $J=13.1, 5.3$ Hz, CH_2Ar), 2.80 (1H, dd, $J=13.0, 4.0$ Hz, CH_2Ar), 2.60 (7H, s, NHCH_3 and $\text{CH}_2\text{CH}_2\text{CO}_2\text{Me}$), 2.42 (3H, m, SCH_2CH), 2.11 (1H, m, iBuCH), 1.49 (1H, m, Me_2CHCH_2), 1.28 (1H, m, Me_2CHCH_2), 0.97 (1H, m, Me_2CHCH_2), 0.82 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.75 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$).

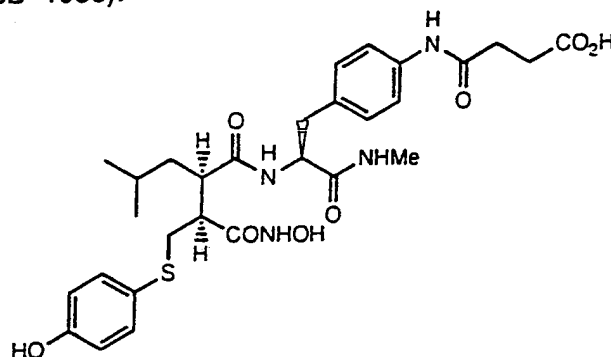
b) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenylthiomethyl)-succinyl]-L-(4-N-(methyl succinylamido)- phenylalanine-N-methylamide

[4-Hydroxy-2R-isobutyl-3S-(4-hydroxyphenylthiomethyl)-succinyl]-L-4-(N-methylsuccinylamido)-phenylalanine-N-methylamide (0.95g, 1.58 mmol) was coupled with hydroxylamine as described in example 12d to produce the title compound (0.40g, 0.64 mmol, 41%): $^1\text{H-NMR}$; δ (Methanol- d_4), 7.47 (1H, d, $J=8.3$ Hz, Aryl-H), 7.19 (2H, d, $J=8.4$ Hz, Aryl-H), 6.92 (2H, d, $J=8.6$ Hz, Aryl-H), 6.61 (2H, d, $J=8.4$ Hz, Aryl-H), 4.56 (1H, m, NHCHCO), 3.57 (3H, s, CO_2CH_3), 3.01 (1H, m, CHCH_2Ar), 2.80 (1H, m, CHCH_2Ar), 2.64

(4H, m, $\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$), 2.56 (3H, s, CONHCH_3), 2.50 (2H, m, CHCH_2S and iBuCH), 2.06 (2H, m, CHCH_2S), 1.29 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.95 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.81 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.73 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$); ^{13}C NMR: δ (Methanol- d_4), 172.3, 172.1, 170.9, 168.9, 167.9, 137.2, 132.0, 131.9, 128.7, 123.4, 117.9, 115.3, 53.7, 50.8, 48.7, 39.4-38.7, 36.5, 35.2, 30.4, 28.1, 25.0, 24.6, 23.6 and 21.0.

Example 17

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenylthiomethyl)-succinyl]-L-(4-N-(4-(4-oxobutanoic acid)-aminophenylalanine-N-methylamide (BB 1036).

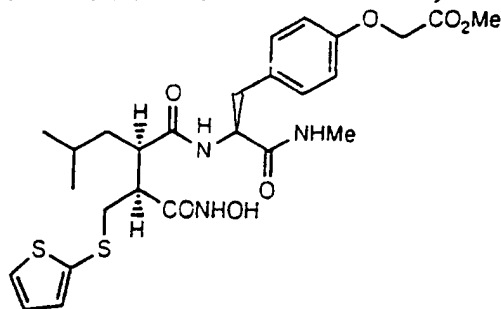


[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenylthiomethyl)-succinyl]-L-(4-N-(methyl succinylamido)-phenylalanine-N-methylamide (153mg, 0.25mmol) was treated with lithium hydroxide as described in example 13 to give the title compound (150mg, 0.24 mmol, 99%): ^1H -NMR; δ (Methanol- d_4), 7.47 (2H, d, $J=8.3$ Hz, Aryl-H), 7.19 (2H, d, $J=8.3$ Hz, Aryl-H), 6.92 (2H, d, $J=8.6$ Hz, Aryl-H), 6.61 (2H, d, $J=8.6$ Hz, Aryl-H), 4.57 (1H, m, NHCHCO), 2.96 (1H, m, CHCH_2Ar), 2.81 (1H, m, CHCH_2Ar), 2.65 (4H, m, $\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$), 2.48 (5H, s, CONHCH_3 , CHCH_2S and iBuCH), 2.10 (2H, m, CHCH_2S), 1.36 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.97 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.77 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.73 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$); ^{13}C NMR: δ (Methanol- d_4), 180.1, 175.5, 173.9, 173.8, 171.4, 157.8, 139.0, 134.6, 133.9, 130.6, 125.5, 120.9, 117.0, 56.20, 50.01-47.8, 41.5, 38.5, 36.2, 34.5, 33.8, 26.9, 26.2, 24.5 and 21.7.

Example 18

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-

4-(oxymethylcarboxymethyl)-phenylalanine-N-methylamide (BB 943)



a) N-Boc-Tyrosine-N-methylamide.

N-Boc-O-benzyltyrosine-N-methylamide (44.3g, 115 mmol) was dissolved in 10% cyclohexene/ethanol (500 mL), 10% palladium on charcoal (4.5g) added and the mixture refluxed for 3 hours. Filtration to remove the catalyst and solvent removal gave the title compound (30.8g, 105 mmol, 91%).

b) N-Boc-4-(oxymethylcarboxybenzyl)phenylalanine-N-methylamide.

N-Boc-Tyrosine-N-methylamide (30.7g, 104 mmol) was dissolved in acetone (anhydrous, 500 mL), sodium carbonate (13.3g, 125 mmol) and benzylbromoacetate (35.9g, 157 mmol) were added and the mixture refluxed under argon for 4 days. The mixture was filtered, the solvent removed and the residual oil purified by column chromatography using methanol/DCM (2%) as eluant to give the title compound (36.1g, 81.7 mmol, 78%).

c) N-Boc-4-(oxymethylcarboxymethyl)phenylalanine-N-methylamide.

N-Boc-4-(oxymethylcarboxybenzyl)phenylalanine-N-methylamide (19.7g, 55.8 mmol) was taken up in 10% cyclohexene/ethanol (250 mL), 10% palladium on charcoal (2.6 g) added and the mixture refluxed for one hour. Removal of the catalyst by filtration then evaporation of the solvents gave the acid as a white foam (19.7g, 55.8 mmol, 98%). This crude acid was dissolved in DMF (200 mL) and stirred at 0° while potassium carbonate (8.48g, 61 mmol) and methyl iodide (5.21 mL, 83.6 mmol) were added. The mixture was stirred at 0° for 2 hours and at room temperature for one hour. The reaction was filtered to remove inorganic solids, the DMF evaporated under vacuum, then the residue taken up in DCM. The organic layer was washed with brine, dried over magnesium sulphate and finally

the solvent removed to give the title ester as a white solid (18.5g, 50.5 mmol, 91%): $^1\text{H-NMR}$; δ (CDCl_3), 7.11 (2H, d, $J = 8.6$ Hz, Aryl-H), 6.83 (2H, d, $J = 8.6$ Hz, Aryl-H), 6.03 (1H, m, NHMe), 5.14 (1H, bd, NH^tBoc), 4.60 (2H, s, $\text{CH}_2\text{CO}_2\text{Me}$), 4.25 (1H, q, $J = 7.0$ Hz), 3.80 (3H, s, CO_2CH_3), 2.98 (2H, bd, $J = 7$ Hz, CH_2Ar), 2.71 (3H, d, NHCH_3), and 1.40 (9H, s, $\text{C}(\text{CH}_3)_3$).

d) [4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-L-4-(oxymethylcarboxymethyl)phenylalanine-N-methylamide.

N-Boc-4-(oxymethylcarboxymethyl)phenylalanine-N-methylamide (18.5g, 50.5 mmol) was taken up in DCM/TFA (1:1, 100 mL) and left overnight at 4° . Solvent removal gave the amine as the TFA salt contaminated with excess TFA. This mixture was dissolved in DMF (100 mL), cooled to 0° . NMM (14.6g, 145 mmol) and benzyl (2-benzyloxycarbonyl-5-methyl-3R-pentafluorophenoxycarbonyl)-hexanoate (85.5g, 150 mmol) were added and the reaction stirred at room temperature for 72 hours. The DMF was removed under vacuum and the residual oil taken up in DCM, washed with 2M sodium carbonate, 2M hydrochloric acid and saturated brine then dried over magnesium sulphate. The solution was filtered, the solvent evaporated and the resultant oil purified by column chromatography (silica gel, 30 - 53% ethyl acetate in DCM) to give the title compound as a white foam (17.6 g, 27.3 mmol, 54%): $^1\text{H-NMR}$; δ (CDCl_3), 7.40 - 7.17 (10H, m, $\text{CO}_2\text{CH}_2\text{Ph}$), 7.12 (2H, d, $J = 8.6$ Hz, Aryl-H), 6.82 (2H, d, $J = 8.6$ Hz, Aryl-H), 6.67 (1H, d, $J = 7.8$ Hz, NHCH), 5.94 (1H, m, NHMe), 5.22 - 5.04 (3H, m, $\text{CO}_2\text{CH}_2\text{Ph}$ and $\text{CH}(\text{CO}_2\text{CH}_2\text{Ph})_2$), 4.60 (2H, s, $\text{CH}_2\text{CO}_2\text{Me}$), 4.48 (1H, q, $J = 7.0$ Hz), 3.80 (3H, s, CO_2CH_3), 3.02 - 2.90 (3H, m, CH_2Ar , and $^t\text{BuCH}$), 2.65 (3H, d, $J = 4.7$ Hz, NHCH_3), 1.54 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 1.35 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 1.04 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.76 (3H, d, $J = 6.5$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.74 (3H, d, $J = 6.5$ Hz, $\text{CH}(\text{CH}_3)_2$).

e) [Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-4-(oxymethylcarboxymethyl)-phenylalanine-N-methylamide

[4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-L-4-(oxymethylcarboxymethyl)phenylalanine-N-methylamide (17.6g, 27.3 mmol) was treated as described in example 12b to yield the title compound (6.70g, 15.4 mmol, 56%): $^1\text{H-NMR}$; δ (Methanol- d_4), 7.78 (1H, bd, $J = 7.2$ Hz, CONHCH), 7.10 - 6.75 (5H, m, Aryl-H and NHMe), 6.19 (1H, d, $J = 3.0$ Hz, $\text{CH}_2=\text{C}$), 5.58 (1H, d, $J = 3.6$ Hz, $\text{CH}_2=\text{C}$), 4.63 (2H, s, $\text{CH}_2\text{CO}_2\text{Me}$), 4.48 (1H, m, NHCHCO), 3.74 (3H, s, CO_2CH_3), 3.52 (1H, m, $^t\text{BuCH}$), 3.00 - 2.78 (2H,

m, CH_2Aryl), 2.65 (3H, s, NHCH_3), 1.63 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 1.40 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), and 0.87 - 0.80 (7H, m + 2xd, $J=6.5$ Hz, $(\text{CH}_3)_2\text{CHCH}_2$ and $\text{CH}(\text{CH}_3)_2$).

f) [4-Hydroxy-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-4-(oxymethylcarboxymethyl)-phenylalanine-N-methylamide.

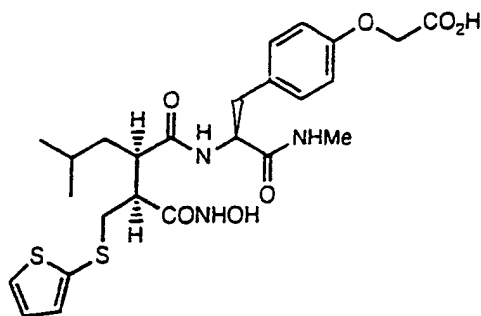
[Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-4-(oxymethylcarboxymethyl)-phenylalanine-N-methylamide (4.77g, 11.0 mmol) was treated with thiophene-2-thiol as described in example 12c to give the title compound as a white solid (1.90g, 3.46 mmol, 31%): $^1\text{H-NMR}$; δ (DMSO- d_6), 8.35 (1H, bq, NHMe) 7.96 (1H, d, $J=8.5$, CONHCH), 7.54 (1H, m, Thienyl-H5), 7.18 (2H, d, $J=8.5$ Hz, Aryl-H), 7.00 (2H, m, Thienyl-H3,4), 6.81 (2H, d, $J=8.5$ Hz, Aryl-H), 4.71 (2H, s, $\text{OCH}_2\text{CO}_2\text{Me}$), 4.40 (1H, m, NCHCO), 3.68 (3H, s, CO_2CH_3), 2.95 - 2.64 (2H, m, CH_2Ar), 2.58 (3H, d, $J=5.0$ Hz, NHCH_3) 2.37 (2H, m, SCH_2CH), 2.14 (1H, s, $i\text{BuCH}$), 1.42 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 1.23 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.99 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.79 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.76 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$).

g) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-(4-N-(oxymethylcarboxymethyl)-phenylalanine-N-methylamide.

[4-Hydroxy-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-4-(oxymethylcarboxymethyl)-phenylalanine-N-methylamide (1.90g, 3.46 mmol) was treated as described in example 12d to give the title compound (0.92g, 1.62 mmol, 47%): $^1\text{H-NMR}$; δ (DMSO- d_6), 10.56 (1H, s, NHOH), 8.89 (1H, s, CONHOH), 8.24 (1H, d, CHCONHCH), 7.79 (1H, m, CONHCH_3), 7.52 (1H, m, Thienyl-H5), 7.17 (2H, d, $J=8.4$ Hz, Aryl-H), 6.93 (2H, m, Thienyl-H3,4), 6.78 (2H, d, $J=8.4$ Hz, Aryl-H), 4.69 (2H, s, $\text{OCH}_2\text{CO}_2\text{Me}$), 4.42 (1H, m, NHCHCO), 3.68 (3H, s, CO_2CH_3), 2.78 (2H, m, CHCH_2Ar), 2.55 (3H, d, $J=4.5$ Hz, CONHCH_3), 2.48 (2H, m, CHCH_2S and $i\text{BuCH}$), 2.08 (2H, m, CHCH_2S), 1.32 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.88 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.78 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.71 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$): $^{13}\text{C-NMR}$; δ (DMSO- d_6), 171.9, 170.9, 168.8, 167.7, 155.7, 133.1, 131.8, 130.5, 130.2, 128.7, 127.2, 113.6, 64.2, 53.7, 51.3, 45.6, 45.3, 40.05-38.1, 37.7, 36.1, 25.0, 24.6, 23.6 and 21.06

Example 19

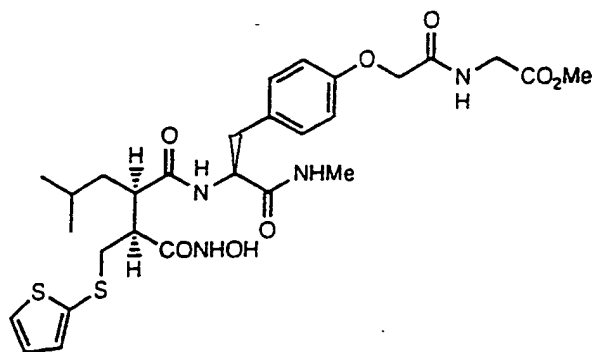
[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-(4-N-(oxymethylcarboxylic acid)-phenylalanine-N-methylamide (BB 944).



[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-(4-N-(oxymethylcarboxymethyl)-phenylalanine-N-methylamide (0.42g, 0.75 mmol) was treated with lithium hydroxide as described in example 13 to give the title compound (0.42g, 0.75 mmol, 100%) as a white solid: ^1H -NMR; δ (D_2O), 7.41 (1H, m, Thienyl-H5), 7.22 (2H, d, $J=8.4$ Hz, Aryl-H), 6.97 (2H, m, Thienyl-H3,4), 6.89 (2H, d, $J=8.4$ Hz, Aryl-H), 4.48 (1H, m, NHCHCO), 4.40 (2H, s, $\text{OCH}_2\text{CO}_2\text{Me}$), 3.05 (1H, m, CHCH_2Ar), 2.74 (1H, m, CHCH_2Ar), 2.65 (3H, d, $J=4.5$ Hz, CONHCH_3), 2.38 (2H, m, CHCH_2S and iBuCH), 2.03 (1H, m, CHCH_2S), 1.78 (1H, m, CHCH_2S), 1.23 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.98 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.78 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.71 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$): ^{13}C NMR: δ (D_2O), 176.9, 175.5, 173.6, 168.3, 157.0, 133.3, 123.4, 130.6, 129.9, 128.0, 115.0, 66.9, 55.4, 46.7, 46.0, 40.0, 36.6, 36.4, 26.0, 25.6, 23.2, and 20.8.

Example 20

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide (BB 888)



a) N-Boc-4-(oxymethylcarboxylic acid)-phenylalanine-N-methylamide

N-Boc-4-(oxymethylcarboxybenzyl)phenylalanine-N-methylamide (35.5g, 80.3 mmol) was dissolved in 20% cyclohexene in ethanol (400 mL), 7.1g 10% palladium on charcoal added and the mixture heated under reflux for 15 minutes. The catalyst was removed by filtration and the solvent evaporated to leave the title compound (28.5g, 80.5 mmol, 100%): $^1\text{H-NMR}$; δ (Methanol- d_4), 7.09 (2H, d, $J=8.6$ Hz, Aryl-H), 6.81 (2H, d, $J=8.6$ Hz, Aryl-H), 4.56 (2H, s, $\text{OCH}_2\text{CO}_2\text{H}$), 4.18 (1H, m, NHCHCO), 2.95 - 2.72 (2H, m, CH_2Ar), 2.62 (3H, s, CONHCH_3), and 1.32 (9H, s, $\text{C}(\text{CH}_3)_3$).

b) N-Boc-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide.

N-Boc-4-(oxymethylcarboxylic acid)-phenylalanine-N-methylamide (7.47g, 21.2 mmol) was taken up in DMF (25 mL) and cooled to 0° . To this solution was added, pentafluorophenol (7.80g, 42.4 mmol), glycine methyl ester (from the hydrochloride salt, 3.19g, 25.4 mmol) and WSCDI (4.88g, 25.4 mmol) and the mixture stirred at room temperature overnight. The solvent was removed by evaporation and the residual oil taken up in DCM which was then sequentially washed with 2M sodium carbonate solution, 2M hydrochloric acid solution and saturated brine. The separated organic layer was dried over magnesium sulphate and the solvent evaporated to leave the title compound (7.08g, 16.7 mmol, 79%): $^1\text{H-NMR}$; δ (CDCl_3), 7.12 (2H, d, $J=8.6$ Hz, Aryl-H), 6.84 (2H, d, $J=8.6$ Hz, Aryl-H), 6.11 (1H, bq, CONHMe), 5.17 (1H, bd, CONHCH), 4.48 (2H, s, $\text{OCH}_2\text{CO}_2\text{H}$), 4.28 (1H, m, NHCHCO), 4.12 (2H, bd, $\text{NHCH}_2\text{CO}_2\text{Me}$), 3.76 (3H, s, CO_2CH_3), 2.96 (2H, m, CH_2Ar), 2.72 (3H, d, $J=4.8$ Hz, CONHCH_3), and 1.38 (9H, s, $\text{C}(\text{CH}_3)_3$).

c) [4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)phenylalanine-N-methylamide.

N-Boc-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide (5.35g, 12.6 mmol) was dissolved in TFA/DCM (1:1, 100 mL) and stood overnight at 4° . Solvent removal gave an oil which was dissolved in DCM and washed with 2M sodium carbonate, dried over magnesium sulphate and the solvent removed to leave the free amine as a yellow solid (3.71g, 11.1 mmol, 88%). This was coupled with benzyl (2-benzyloxycarbonyl-5-methyl-3R-pentafluorophenoxycarbonyl)-hexanoate (12.4g, 21.9 mmol) as described in example 18d to give the title compound (6.60g, 9.38 mmol, 86%): $^1\text{H-NMR}$; δ (CDCl_3), 7.35 - 7.20 (10H, m, Ph), 7.15

(2H, d, $J=8.6$ Hz, Aryl-H), 6.84 (2H, d, $J=8.6$ Hz, Aryl-H), 6.67 (1H, bd, CONHCH), 5.92 (1H, bq, CONHMe), 5.17 - 5.05 (4H, m, $\text{CH}(\text{CO}_2\text{CH}_2\text{Ph})_2$), 4.48 (3H, s + m, $\text{OCH}_2\text{CO}_2\text{H}$ and NHCHCO), 4.12 (2H, bd, $\text{NHCH}_2\text{CO}_2\text{Me}$), 3.80 (1H, d, $J=9.3$ Hz, $\text{CH}(\text{CO}_2\text{CH}_2\text{Ph})_2$), 3.76 (3H, s, CO_2CH_3), 2.97 (2H, m, CH_2Ar), 2.67 (3H, d, $J=4.8$ Hz, CONHCH_3), 1.54 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 1.35 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 1.02 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.76 (3H, d, $J=6.4$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.75 (3H, d, $J=6.4$ Hz, $\text{CH}(\text{CH}_3)_2$).

d) [Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide

[4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)phenylalanine-N-methylamide (7.62g, 10.8 mmol) was treated as described in example 12b to yield the title compound (3.77g, 7.67 mmol, 72%): $^1\text{H-NMR}$; δ (Methanol- d_4), 7.80 (2H, bm, NH), 7.08 (2H, d, $J=8.7$ Hz, Aryl-H), 6.86 (2H, d, $J=8.7$ Hz, Aryl-H), 6.18 (1H, d, $J=3.0$ Hz, $\text{CH}_2=\text{C}$), 5.59 (1H, d, $J=3.6$ Hz, $\text{CH}_2=\text{C}$), 4.49 (2H, s, $\text{OCH}_2\text{CO}_2\text{H}$), 4.45 (1H, m, NHCHCO), 3.99 (2H, s, $\text{NHCH}_2\text{CO}_2\text{Me}$), 3.69 (3H, s, CO_2CH_3), 3.52 (1H, bm, CHCO_2H), 2.88 (2H, m, CH_2Ar), 2.65 (3H, d, $J=4.8$ Hz, CONHCH_3), 1.63 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 1.40 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.86 (3H, d, $J=6.2$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.81 (3H, d, $J=6.3$ Hz, $\text{CH}(\text{CH}_3)_2$).

e) [4-Hydroxy-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide.

[Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide (1.56g, 3.17 mmol) was treated with thiophene-2-thiol as described in example 12c to give the title compound as a white solid (1.30g, 2.14 mmol, 67%): $^1\text{H-NMR}$; δ (Methanol- d_4), 8.39 (1H, bd, $J=8.5$ Hz, NHCH), 7.85 (1H, m, CONHMe), 7.38 (1H, dd, $J=5.3, 1.3$ Hz, Thienyl-H5), 7.21 (2H, d, $J=8.6$ Hz, Aryl-H), 6.98 (1H, dd, $J=3.5, 1.3$ Hz, Thienyl-H3), 6.94 (2H, d, $J=8.7$ Hz, Aryl-H), 6.91 (1H, dd, $J=5.2, 3.5$ Hz, Thienyl-H4), 4.55 (3H, s, $\text{OCH}_2\text{CO}_2\text{H}$ and NHCHCO), 3.96 (2H, s, $\text{NHCH}_2\text{CO}_2\text{Me}$), 3.67 (3H, s, CO_2CH_3), 2.91 (1H, dd, $J=13.9, 5.1$ Hz, CH_2Ar), 2.76 (1H, dd, $J=13.9, 5.1$ Hz, CH_2Ar), 2.66 (3H, s, CONHCH_3), 2.45 (3H, m, SCH_2CH and CHCO_2H), 2.16 (1H, m, SCH_2CH), 1.50 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 1.30 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.98 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.83 (3H, d, $J=6.5$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.76 (3H, d, $J=6.3$ Hz, $\text{CH}(\text{CH}_3)_2$).

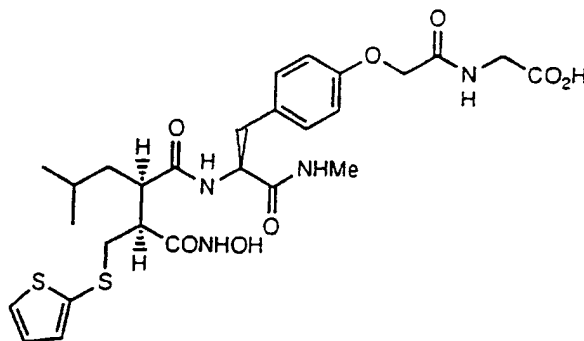
f) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-

L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide

[4-Hydroxy-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide (1.29g, 2.12 mmol) was treated as described in example 12d to give the title compound as a white solid (0.90g, 1.45 mmol, 68%): Anal. calculated for $C_{28}H_{38}N_4O_8S_2$, Requires, C 54.00, H 6.15, N 9.00; Found, C 54.04, H 6.16, N 8.79: 1H -NMR; δ (DMSO- d_6), 10.55 (1H, s, CONHOH), 8.89 (1H, s, CONHOH), 8.45 (1H, m, CONHCH₂), 8.23 (1H, bd, J=8.5 Hz, NHCH), 7.79 (1H, m, CONHMe), 7.51 (1H, dd, J=5.3, 1.3 Hz, Thienyl-H5), 7.19 (2H, d, J=8.6 Hz, Aryl-H), 6.95 (2H, m, Thienyl-H3,4), 6.83 (2H, d, J=8.5 Hz, Aryl-H), 4.47 (2H, s, OCH₂CO₂Me), 4.45 (1H, m, NHCHCO), 3.92 (2H, s, NHCH₂CO₂Me), 3.63 (3H, s, CO₂CH₃), 2.88 (1H, m, SCH₂CH), 2.62 (2H, m, CH₂Ar), 2.53 (3H, d, J=4.5 Hz, CONHCH₃), 2.39 (1H, m, iBuCH), 2.16 (1H, m, SCH₂CH), 1.99 (1H, m, SCH₂CH), 1.31 (2H, m, (CH₃)₂CHCH₂), 0.83 (1H, m, (CH₃)₂CHCH₂), 0.80 (3H, d, J=6.6 Hz, CH(CH₃)₂), and 0.76 (3H, d, J=6.6 Hz, CH(CH₃)₂): ^{13}C -NMR; δ (DMSO- d_6), 172.4, 171.4, 170.0, 168.3, 167.9, 156.1, 132.3, 130.7, 130.1, 129.2, 127.7, 114.4, 66.8, 54.2, 51.7, 46.0, 45.8, 40.5-38.5, 38.1, 36.6, 25.4, 25.0, 24.0 and 21.5

Example 21

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-4-(oxymethylcarboxyglycine)-phenylalanine-N-methylamide (BB 899).

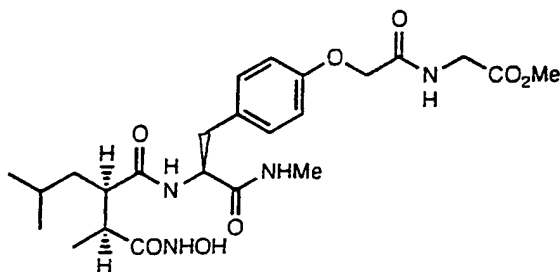


[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide (0.45g, 0.73 mmol) was treated with lithium hydroxide as described in example 13 to give the title compound (0.41g, 0.67 mmol, 92%): 1H -NMR; δ (D₂O), 7.43 (1H, dd, J=5.3, 1.3 Hz, Thienyl-H5), 7.28 (2H, d, J=8.5 Hz, Aryl-

H), 7.06 (2H, d, $J=8.5$ Hz, Aryl-H), 6.95 (1H, m, Thienyl-H3), 6.83 (1H, m, Thienyl-H4), 4.70 (1H, m, NHCHCO), 4.58 (2H, s, NHCH_2CONH), 3.63 (2H, bs, $\text{NHCH}_2\text{CO}_2\text{H}$), 3.12 (1H, m, CH_2Ar), 2.79 (1H, m, CH_2Ar), 2.68 (3H, s, CONHCH_3), 2.21 (2H, m, SCH_2CH and $i\text{BuCH}$), 2.05 (1H, m, SCH_2CH), 1.65 (1H, m, SCH_2CH), 1.19 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.91 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.81 (3H, d, $J=6.6$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.76 (3H, d, $J=6.6$ Hz, $\text{CH}(\text{CH}_3)_2$): ^{13}C -NMR; δ (D_2O), 195.6, 176.6, 175.5, 173.8, 171.6, 156.7, 132.8, 132.2, 130.8, 130.6, 129.7, 128.1, 115.5, 66.9, 55.3, 46.8, 46.0, 42.8, 40.0, 36.7, 36.3, 26.5, 26.1, 23.5 and 20.1.

Example 22

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-succinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide (BB 877)



a) [4-(N-Benzyloxyamino)-2R-isobutyl-3S-methyl-succinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide

[Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide (1.05g, 2.14 mmol) was dissolved in ethanol (40 mL), 10% palladium on charcoal added and the mixture subjected to an atmosphere of hydrogen for one hour. The catalyst was removed by filtration and solvent removal gave the saturated compound as a solid (0.99g, 2.00 mmol, 93%). This material (0.97g, 1.96 mmol) was dissolved in DMF/DCM (20%, 10 mL), pentafluorophenol (0.72g, 3.93 mmol), O-benzylhydroxylamine (0.48g, 3.93 mmol), NMM (0.26g, 2.55 mmol) and WSCDI (0.49g, 2.55 mmol) added and the reaction mixture stirred overnight. The precipitated solid was filtered off and the solvent removed from the filtrate to leave a solid which was washed with 1M hydrochloric acid and ethyl acetate. The combined solids were recrystallised from methanol to give the title benzhydroxamate (0.42g,

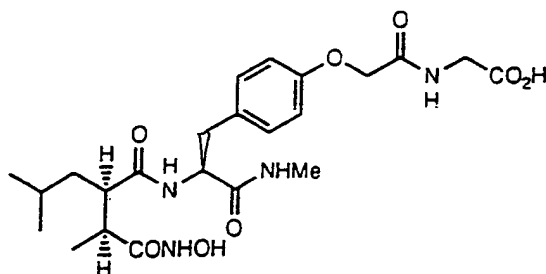
0.70 mmol, 36%): $^1\text{H-NMR}$; δ (DMSO-d_6), 10.98 (1H, s, CONHOBn), 8.48 (1H, m, NHCH_2), 8.15 (1H, d, $J=9$ Hz, NHCH), 7.73 (1H, m, CONHMe), 7.36 (5H, s, Ph), 7.19 (2H, d, $J=8.6$ Hz, Aryl-H), 6.86 (2H, d, $J=8.7$ Hz, Aryl-H), 4.74 (2H, s, CH_2Ph), 4.46 (3H, s, $\text{OCH}_2\text{CO}_2\text{Me}$ and NHCHCO), 3.90 (2H, d, $J=5.6$ Hz, $\text{NHCH}_2\text{CO}_2\text{Me}$), 3.63 (3H, s, CO_2CH_3), 2.89 (1H, m, CH_2Ar), 2.73 (1H, m, CH_2Ar), 2.56 (3H, d, $J=4.5$ Hz, CONHCH_3), 2.37 (1H, m, CHCONHOBn), 1.91 (1H, m, $i\text{BuCH}$), 1.30 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.83 (3H, d, $J=6.3$ Hz, $\text{CH}(\text{CH}_3)_2$), 0.72 (3H, d, $J=6.3$ Hz, $\text{CH}(\text{CH}_3)_2$), 0.71 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), and 0.45 (3H, d, $J=6.6$ Hz, CHCH_3).

b) [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-succinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide

[4-(N-Benzoyloxyamino)-2R-isobutyl-3S-methyl-succinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide (0.42g, 0.70 mmol) was hydrogenated as described in example 10c to give the title compound as a solid (0.29g, 0.57 mmol, 82%): Anal. calculated for $\text{C}_{24}\text{H}_{36}\text{N}_4\text{O}_8$: Requires, C 56.86, H 7.13, N 11.02; Found, C 56.14, H 7.08, N 10.60: $^1\text{H-NMR}$; δ (DMSO-d_6), 8.70 (1H, s, CONHOH), 8.49 (1H, m, NHCH_2), 8.18 (1H, d, $J=8.5$ Hz, NHCH), 7.73 (1H, m, CONHMe), 7.19 (2H, d, $J=8.5$ Hz, Aryl-H), 6.85 (2H, d, $J=8.6$ Hz, Aryl-H), 4.47 (1H, m, NHCHCO), 4.48 (2H, s, $\text{OCH}_2\text{CO}_2\text{Me}$), 3.89 (2H, d, $J=5.9$ Hz, $\text{NHCH}_2\text{CO}_2\text{Me}$), 3.63 (3H, s, CO_2CH_3), 2.89 (1H, m, CH_2Ar), 2.69 (1H, m, CH_2Ar), 2.58 (3H, d, $J=4.5$ Hz, CONHCH_3), 2.39 (1H, m, CHCONHOBn), 1.98 (1H, m, $i\text{BuCH}$), 1.32 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.88 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.83 (3H, d, $J=6.5$ Hz, $\text{CH}(\text{CH}_3)_2$), 0.72 (3H, d, $J=6.5$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.48 (3H, d, $J=6.6$ Hz, CHCH_3): $^{13}\text{C-NMR}$; δ (DMSO-d_6), 172.8, 171.1, 170.7, 169.6, 167.9, 155.7, 130.6, 129.7, 113.9, 66.6, 53.7, 51.3, 46.2, 39.9-38.0, 36.1, 25.0, 24.8, 23.6, 21.1 and 15.6.

Example 23

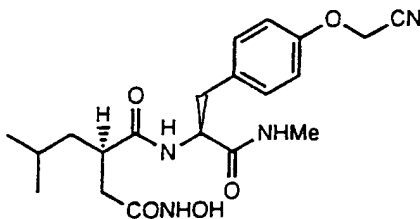
[4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-succinyl]-L-4-(oxymethylcarboxyglycyl)-phenylalanine-N-methylamide



[4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-succinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide (0.11g, 0.22 mmol) was treated with lithium hydroxide as described in example 13 to give the title compound (0.09g, 0.18 mmol, 83%): $^1\text{H-NMR}$; δ (D_2O), 7.19 (2H, d, $J=8.5$ Hz, Aryl-H), 6.92 (2H, d, $J=8.6$ Hz, Aryl-H), 4.56 (2H, s, $\text{OCH}_2\text{CO}_2\text{Me}$), 4.51 (1H, m, NHCHCO), 3.80 (2H, s, $\text{NHCH}_2\text{CO}_2\text{Me}$), 2.96 (2H, m, CH_2Ar), 2.61 (3H, s, CONHCH_3), 2.42 (1H, m, CHCONHOH), 2.11 (1H, m, iBuCH), 1.31 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.95 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.83 (3H, d, $J=6.5$ Hz, $\text{CH}(\text{CH}_3)_2$), 0.75 (3H, d, $J=6.5$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.61 (3H, d, $J=6.6$ Hz, CHCH_3): $^{13}\text{C-NMR}$; δ (D_2O), 195.6, 176.6, 175.5, 173.8, 171.6, 156.7, 132.8, 132.2, 130.8, 130.6, 129.7, 128.1, 115.5, 66.9, 55.3, 46.8, 46.0, 42.8, 40.0, 36.7, 36.3, 26.5, 26.1, 23.5 and 20.1.

Example 24

[4-(N-Hydroxyamino)-2R-isobutyl-succinyl]-L-4-(oxymethylnitrile)-phenylalanine-N-methylamide.



a) [4-t-Butoxy-2R-isobutylsuccinyl]-L-(4-oxymethylnitrile)-phenylalanine-N-methylamide.

[4-t-Butoxy-2R-isobutylsuccinyl]-L-(4-hydroxy)-phenylalanine-N-methylamide (see example 1g, 0.50g, 1.2 mmol) was dissolved in dry methyl ethyl ketone (20 mL) and sodium carbonate (0.16g, 1.48 mmol) was added. Bromoacetonitrile (0.22g, 1.84 mmol) was added dropwise and the

reaction heated at reflux overnight after which time a second aliquot of bromoacetonitrile was added (0.22g, 1.84 mmol) and the mixture heated at reflux for a further 18 hours. The solvents were removed under vacuum and the residue taken up in DCM/hexane and filtered then purified by column chromatography (silica gel, 5% methanol/DCM) to give recovered starting material (0.21g) along with the title compound (0.38g, 0.85 mmol, 71%): $^1\text{H-NMR}$; δ (CDCl_3), 7.08 (2H, d, $J=8.6$ Hz, Aryl-H), 6.76 (2H, d, $J=8.6$ Hz, Aryl-H), 6.34 (1H, d, $J=7.9$ Hz, CONHCH), 5.91 (1H, m, CONHMe), 4.78 (2H, s, OCH_2CN), 4.49 (1H, m, NHCHCO), 3.06 (1H, dd, $J=6.2, 13.8$ Hz, CH_2Ar), 2.97 (1H, dd, $J=7.9, 13.8$ Hz, CH_2Ar), 2.70 (3H, d, $J=4.8$ Hz, CONHMe), 2.61 (1H, m, iBuCH), 2.49 (1H, dd, $J=4.2, 16.1$ Hz, $\text{CH}_2\text{CO}_2\text{iBu}$), 2.40 (1H, dd, $J=4.2, 16.1$ Hz, $\text{CH}_2\text{CO}_2\text{iBu}$), 1.44 (11H, s + m, $\text{C}(\text{CH}_3)_3$ and $(\text{CH}_3)_2\text{CHCH}_2$), 1.25 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.87 (3H, d, $J=6.4$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.84 (3H, d, $J=6.4$ Hz, $\text{CH}(\text{CH}_3)_2$).

b) [4-(N-Benzyloxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylnitrile)-phenylalanine-N-methylamide.

[4-t-Butoxy-2R-isobutylsuccinyl]-L-(4-oxymethylnitrile)-phenylalanine-N-methylamide (0.38g, 0.98 mmol) was dissolved in 95% TFA/water and stirred at 0° for 3 hours after which time tlc indicated complete conversion to the acid. Removal of the solvents gave the crude acid which was taken up in DCM (5mL), pentafluorophenol (0.36g, 1.95 mmol), O-benzylhydroxylamine (0.24g, 1.95 mmol), NMM (0.15g, 1.47 mmol) and WSCDI (0.26g, 1.37 mmol) added, and the reaction mixture stirred overnight. The precipitated product was collected by filtration and washed with DCM and dried to give the title compound (0.21g, 0.47 mmol, 48%): $^1\text{H-NMR}$; δ (Methanol- d_4), 8.17 (1H, d, $J=7.9$ Hz, CONHCH), 7.91 (1H, m, CONHMe), 7.36 (5H, s, Ph), 7.36 (2H, d, $J=8.6$ Hz, Aryl-H), 6.90 (2H, d, $J=8.6$ Hz, Aryl-H), 4.85 (2H, s, OCH_2Ph), 4.77 (2H, s, OCH_2CN), 4.45 (1H, m, NHCHCO), 3.10 (1H, dd, $J=6.9, 14.4$ Hz, CH_2Ar), 2.87 (1H, dd, $J=8.9, 13.8$ Hz, CH_2Ar), 2.66 (4H, d + m, $J=4.6$ Hz, CONHMe and iBuCH), 2.16 (1H, dd, $J=8.2, 14.6$ Hz, $\text{CH}_2\text{CO}_2\text{iBu}$), 2.01 (1H, dd, $J=6.4, 14.5$ Hz, $\text{CH}_2\text{CO}_2\text{iBu}$), 1.32 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 1.06 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.81 (3H, d, $J=6.4$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.77 (3H, d, $J=6.4$ Hz, $\text{CH}(\text{CH}_3)_2$).

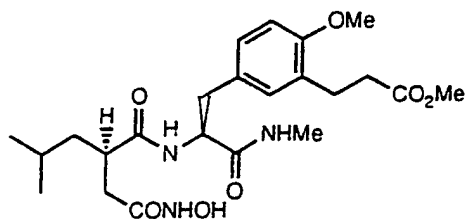
c) [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-4-(oxymethylnitrile)-phenylalanine-N-methylamide.

[4-(N-Benzyloxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylnitrile)-

phenylalanine-N-methylamide (0.21g, 0.47 mmol) was hydrogenated as described in example 10c and purified by recrystallisation from methanol/diethyl ether (0.10g, 0.25 mmol, 53%): $^1\text{H-NMR}$; δ (Methanol- d_4), 7.18 (2H, d, $J=8.7$ Hz, Aryl-H), 6.92 (2H, d, $J=8.7$ Hz, Aryl-H), 4.90 (2H, s, OCH_2CN), 4.42 (1H, m, NHCHCO), 3.12 (1H, m, CH_2Ar), 2.64 (4H, s + m, CONHMe and $i\text{BuCH}$), 2.18 (1H, dd, $J=8.0, 14.6$ Hz, $\text{CH}_2\text{CO}_2i\text{Bu}$), 2.06 (1H, dd, 6.5, 14.5 Hz, $\text{CH}_2\text{CO}_2i\text{Bu}$), 1.33 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 1.07 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.81 (3H, d, $J=6.4$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.77 (3H, d, $J=6.4$ Hz, $\text{CH}(\text{CH}_3)_2$): $^{13}\text{C-NMR}$; δ (Methanol- d_4), 177.1, 174.0, 171.1, 158.0, 133.1, 131.6, 115.8, 56.3, 54.5, 42.6, 37.4, 36.8, 26.8, 26.3, 23.5, and 22.3.

Example 25

[4-(N-Hydroxyamino)-2R-isobutyl-succinyl]-L-3-(1-(2-methoxycarbonyl)-ethyl)-4-methoxy-phenylalanine-N-methylamide (BB 708).



a) [4-tert-Butoxy-2R-isobutyl-succinyl]-L-3-(1-(2-methoxycarbonyl)-ethene)-4-methoxy-phenylalanine-N-methylamide.

[4-tert-Butoxy-2R-isobutyl-succinyl]-L-3-iodo-4-methoxy-phenylalanine-N-methylamide (0.50g, 0.92 mmol) was dissolved in dry acetonitrile (1.5 mL) under argon and methyl acrylate (0.10 mL, 1.15 mmol), triethylamine (0.16 mL, 1.15 mmol), tris-*o*-tolylphosphine (0.07g, 0.23 mmol) and palladium acetate (26 mg, 0.115 mmol) were added, the tube was sealed and heated to 90° overnight. The reaction mixture was cooled, dissolved in ethyl acetate and washed with water. The organic layer was dried over magnesium sulphate, filtered and the solvent removed to give a brown solid which was purified by chromatography on silica gel using ethyl acetate as eluant (0.36g, 0.71mmol, 78%): $^1\text{H-NMR}$; δ (CDCl_3), 7.95 (1H, d, $J=16.2$ Hz, $\text{ArCHCHCO}_2\text{Me}$), 7.37 (1H, m, Aryl-H), 7.23 (1H, m, Aryl-H), 6.85 (1H, d, $J=8.5$ Hz, Aryl-H3), 6.54 (1H, d, $J=16.2$ Hz, $\text{ArCHCHCO}_2\text{Me}$), 6.28 (1H, d, $J=7.7$ Hz, NHCH), 6.01 (1H, m, CONHMe), 4.51 (1H, dd, $J=7.5, 6.5$ Hz, NHCHCO), 3.87 (3H, s, OCH_3), 3.80 (3H, s, CO_2CH_3), 3.06 (2H, m, CH_2Ar), 2.72 (3H, d, $J=4.7$ Hz, CONHCH_3), 2.61 - 2.34 (3H, m, $\text{CH}_2\text{CO}_2i\text{Bu}$ and $i\text{BuCH}$), 1.43

(11H, s + m, C(CH₃)₃ and (CH₃)₂CHCH₂), 1.20 (1H, m, (CH₃)₂CHCH₂), 0.87 (3H, d, J=6.3 Hz, CH(CH₃)₂), and 0.83 (3H, d, J=6.3 Hz, CH(CH₃)₂).

b) [4-(N-Benzyloxyamino)-2R-isobutyl-succinyl]-L-3-(1-(2-methoxycarbonyl)-ethene)-4-methoxy-phenylalanine-N-methylamide.

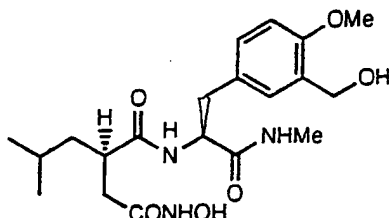
[4-tert-Butoxy-2R-isobutyl-succinyl]-L-3-(1-(2-methoxycarbonyl)-ethene)-4-methoxy-phenylalanine-N-methylamide (300 mg, 0.60 mmol) was dissolved in DCM (3 mL) and TFA (3 mL) added dropwise and the mixture stood at 4° overnight. Solvent removal gave the acid as a solid which was recrystallised from ethanol/diethyl ether (m.p. 176 -177°). This crude acid was coupled with O-benzylhydroxylamine in the presence of pentafluorophenol as described in example 24b to give the benzhydroxamate (200 mg, 0.36 mmol, 61%): ¹H-NMR; δ (CDCl₃), 7.90 (1H, d, J=16.1 Hz, ArCHCHCO₂Me), 7.36 (6H, m, Aryl-H and Ph), 7.18 (1H, dd, J=6.4, 2.1 Hz, Aryl-H), 6.80 (1H, d, J=8.5 Hz, Aryl-H3), 6.69 (1H, bs, CONH), 6.52 (1H, d, J=16.1 Hz, ArCHCHCO₂Me), 6.28 (1H, m, CONHMe), 4.87 (2H, s, OCH₂Ph), 4.55 (1H, q, J=7.5 Hz, NHCHCO), 3.81 (3H, s, OCH₃), 3.78 (3H, s, CO₂CH₃), 3.02 (2H, m, CH₂Ar), 2.71 (3H, d, J=4.7 Hz, CONHCH₃), 2.71 (2H, m, CH₂CO₂tBu), 2.18 (1H, m, tBuCH), 1.44 (2H, m, (CH₃)₂CHCH₂), 1.20 (1H, m, (CH₃)₂CHCH₂), 0.85 (3H, d, J=6.3 Hz, CH(CH₃)₂), and 0.80 (3H, d, J=6.3 Hz, CH(CH₃)₂).

c) [4-(N-Hydroxyamino)-2R-isobutyl-succinyl]-L-3-(1-(2-methoxycarbonyl)-ethyl)-4-methoxy-phenylalanine-N-methylamide

[4-(N-Benzyloxyamino)-2R-isobutyl-succinyl]-L-3-(1-(2-methoxycarbonyl)-ethene)-4-methoxy-phenylalanine-N-methylamide (200 mg, 0.36 mmol) was hydrogenated as described in example 10c to yield the title compound (73 mg, 43%): M.p. 173°: Found: C, 59.34, H, 7.57, N, 8.89%. C₂₃H₃₅N₃O₇ requires C, 59.34, H, 7.58, N, 9.03%: ν_{max} (KBr), 3300, 3000, 1750, and 1640 cm⁻¹: ¹H-NMR; δ (Methanol-d₄), 6.98 (2H, m, Aryl-H), 6.79 (1H, d, J=8.2 Hz, Aryl-H3), 4.43 (1H, dd, J=6.5, 2.2 Hz, NHCHCO), 3.75 (3H, s, OCH₃), 3.60 (3H, s, CO₂CH₃), 3.03 (1H, dd, J=6.4, 7.4 Hz, CH₂Ar), 2.85 - 2.60 (7H, m + s, 2XCH₂ and CONHCH₃), 2.52 (2H, m, CH₂CO₂tBu), 2.06 (2H, bm), 1.05 (1H, m, (CH₃)₂CHCH₂), 0.80 (3H, d, J=6.3 Hz, CH(CH₃)₂), and 0.76 (3H, d, J=6.3 Hz, CH(CH₃)₂): ¹³C-NMR; δ (Methanol-d₄), 177.1, 175.5, 174.0, 170.6, 157.7, 131.7, 130.4, 129.8, 129.5, 111.3, 56.3, 55.8, 52.0, 42.7, 42.4, 37.9, 35.0, 27.1, 26.8, 26.3, 23.5 and 22.3.

Example 26

[4-(N-Hydroxyamino)-2R-isobutyl-succinyl]-L-3-(hydroxymethyl)-4-methoxy-phenylalanine-N-methylamide (BB 792).



a) [4-tert-Butoxy-2R-isobutyl-succinyl]-L-3-(hydroxymethyl)-4-methoxy-phenylalanine-N-methylamide.

[4-tert-Butoxy-2R-isobutyl-succinyl]-L-3-(1-(2-methoxycarbonyl)-ethene)-4-methoxy-phenylalanine-N-methylamide (see example 25a, 300 mg, 0.6 mmol) was dissolved in methanol, cooled to -78° and a stream of ozone passed through for 40 minutes. The solution was warmed to 0° and argon bubbled through for 15 minutes then sodium borohydride (57 mg, 1.5 mmol) added and the solution warmed to room temperature over an hour. Water was added to quench excess borohydride then the solvents removed under reduced pressure and the residue taken up in DCM. The organic layer was washed with brine then dried over magnesium sulphate then the solvent removed to leave the title compound as a white solid (240mg, 0.54 mmol, 90%): $^1\text{H-NMR}$; δ (CDCl_3), 7.18 (1H, d, $J = 2.1$ Hz, Aryl-H), 7.03 (1H, dd, $J = 8.4, 2.1$ Hz, Aryl-H), 6.75 (3H, m, CONHCH , Aryl-H and CONHMe), 4.60 (3H, bm, CH_2OH and NHCHCO), 3.76 (3H, s, OCH_3), 3.30 (1H, bs, OH), 2.99 (2H, m, CH_2Ar), 2.66 (3H, d, $J = 4.7$ Hz, CONHCH_3), 2.62 - 2.23 (3H, m, $\text{CH}_2\text{CO}_2\text{tBu}$ and tBuCH_2), 1.38 (11H, s + m, $\text{C}(\text{CH}_3)_3$ and $(\text{CH}_3)_2\text{CHCH}_2$), 1.20 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.83 (3H, d, $J = 6.3$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.76 (3H, d, $J = 6.3$ Hz, $\text{CH}(\text{CH}_3)_2$).

b) [4-(N-Benzyloxyamino)-2R-isobutyl-succinyl]-L-3-(hydroxymethyl)-4-methoxy-phenylalanine-N-methylamide.

[4-tert-Butoxy-2R-isobutyl-succinyl]-L-3-(hydroxymethyl)-4-methoxy-phenylalanine-N-methylamide (249 mg, 0.53 mmol) was treated with TFA/DCM as described in example 25b to give the acid which was purified by recrystallisation from ethyl acetate/hexane (m.p. $146 - 147^{\circ}$, 200mg, 0.50 mmol, 94%). This acid was coupled to O-benzylhydroxylamine as

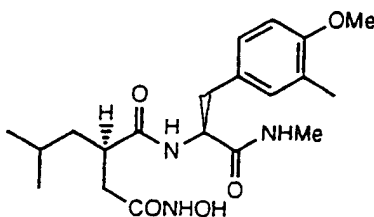
described in example 24b to yield the benzhydroxamate (130mg, 0.27 mmol, 54%): $^1\text{H-NMR}$; δ (DMSO- d_6), 11.00 (1H, s, CONH OH), 8.05 (1H, bd, NHCH), 7.81 (1H, m, CONHMe), 7.40 (5H, s, Ph), 7.23 (1H, bs, Aryl-H), 7.03 (1H, bm, Aryl-H), 6.80 (1H, m, Aryl-H), 4.75 (2H, bs, OCH $_2$ Ph), 4.40 (3H, bm, CH $_2$ OH and NHCHCO), 3.72 (3H, s, OCH $_3$), 3.00 - 2.60 (2H, m, CH $_2$ Ar), 2.60 - 2.40 (5H, m, CH $_2$ CO $_2$ iBu and CONHCH $_3$), 2.05 (1H, m, iBuCH), 1.27 (2H, m, (CH $_3$) $_2$ CHCH $_2$), 0.98 (1H, m, (CH $_3$) $_2$ CHCH $_2$), 0.78 (3H, bd, CH(CH $_3$) $_2$), and 0.73 (3H, d, CH(CH $_3$) $_2$).

c) [4-(N-Hydroxyamino)-2R-isobutyl-succinyl]-L-3-(hydroxymethyl)-4-methoxy-phenylalanine-N-methylamide.

[4-(N-Benzoyloxyamino)-2R-isobutyl-succinyl]-L-3-(hydroxymethyl)-4-methoxy-phenylalanine-N-methylamide (130 mg, 0.27 mmol) was hydrogenated as described in example 10c to yield the title compound (42mg, 0.10 mmol, 38%): $^1\text{H-NMR}$; δ (Methanol- d_4), 7.19 (1H, s, Aryl-H), 7.06 (1H, dd, J=6.2, 2.1 Hz, Aryl-H), 6.80 (1H, m, Aryl-H), 4.55 (2H, s, CH $_2$ OH) 4.44 (1H, dd, J=6.3, 2.3 Hz, NHCHCO), 3.76 (3H, s, OCH $_3$), 3.10 - 2.81 (2H, m, CH $_2$ Ar), 2.65 (4H, s + m, iBuCH and CONHCH $_3$), 2.22 - 2.04 (2H, m, CH $_2$ CONHOH), 1.38 (2H, m, (CH $_3$) $_2$ CHCH $_2$), 1.08 (1H, m, (CH $_3$) $_2$ CHCH $_2$), 0.81 (3H, d, J=6.5 Hz, CH(CH $_3$) $_2$), and 0.75 (3H, d, J=6.5 Hz, CH(CH $_3$) $_2$): $^{13}\text{C-NMR}$; δ (Methanol- d_4), 176.6, 173.8, 156.9, 130.2, 129.9, 129.6, 110.8, 60.1, 56.0, 55.5, 42.2, 42.0, 37.7, 36.4, 26.4, 26.0 and 23.2.

Example 27

[4-(N-Hydroxyamino)-2R-isobutyl-succinyl]-L-3-methyl-4-methoxy-phenylalanine-N-methylamide (BB 804).



a) [4-tert-Butoxy-2R-isobutyl-succinyl]-L-3-methyl-4-methoxy-phenylalanine-N-methylamide.

[4-tert-Butoxy-2R-isobutyl-succinyl]-L-3-(1-(2-methoxycarbonyl)-

ethene)-4-methoxy-phenylalanine-N-methylamide (see example 25a, 300 mg, 0.6 mmol) was dissolved in methanol, cooled to -78° and a stream of ozone passed for 30 minutes. Dimethyl sulphide (56mg, 0.9 mmol) in DCM (10 mL) was added and the mixture warmed to 0° . The solvents were removed under vacuum the residue dissolved in DCM and washed with water. The organic layer was dried over magnesium sulphate, filtered and the solvent removed to leave a crude solid which was purified by recrystallisation from ethyl acetate (200mg, 0.46 mmol, 77%): $^1\text{H-NMR}$; δ (CDCl_3), 6.97 (2H, bs, Aryl-H), 6.70 (1H, d, $J=8.8$ Hz, Aryl-H), 6.46 (1H, d, $J=8.7$ Hz, CONHCH), 6.26 (1H, bm, CONHMe), 4.51 (1H, q, $J=7.2$ Hz, NHCHCO), 3.77 (3H, s, OCH_3), 3.00 (2H, m, CH_2Ar), 2.68 (3H, d, $J=4.7$ Hz, CONHCH_3), 2.67 - 2.28 (3H, m, $\text{CH}_2\text{CO}_2^t\text{Bu}$ and $^t\text{BuCH}$), 2.15 (3H, s, Aryl- CH_3), 1.41 (11H, s + m, $\text{C}(\text{CH}_3)_3$ and $(\text{CH}_3)_2\text{CHCH}_2$), 1.17 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.83 (3H, d, $J=6.3$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.78 (3H, d, $J=6.3$ Hz, $\text{CH}(\text{CH}_3)_2$).

b) [4-(N-Benzyloxyamino)-2R-isobutyl-succinyl]-L-3-methyl-4-methoxy-phenylalanine-N-methylamide.

[4-tert-Butoxy-2R-isobutyl-succinyl]-L-3-methyl-4-methoxy-phenylalanine-N-methylamide (200mg, 0.46 mmol) was deprotected with TFA as described in 25b to yield the acid (110mg, 0.29 mmol, 63%) which was coupled with O-benzylhydroxylamine as described in example 24b to yield the title compound as a white crystalline solid (70 mg, 0.14 mmol, 56%): $^1\text{H-NMR}$; δ (CDCl_3), 8.54 (1H, bs, CONHOBN), 7.37 (5H, bs, Ph), 6.98 (2H, m, Aryl-H), 6.73 (1H, d, $J=8.9$ Hz, Aryl-H), 6.46 (1H, bd, CONHCH), 5.88 (1H, bm, CONHMe), 4.87 (2H, s, OCH_2Ph), 4.47 (1H, dd, $J=7.7, 6.4$ Hz, NHCHCO), 3.79 (3H, s, OCH_3), 3.08 - 2.94 (2H, m, CH_2Ar), 2.70 (4H, d + m, $J=4.7$ Hz, CONHCH_3 and $\text{CH}_2\text{CO}_2^t\text{Bu}$), 2.25 (1H, m, $\text{CH}_2\text{CO}_2^t\text{Bu}$), 2.18 (3H, s, Aryl- CH_3), 1.46 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 1.23 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.89 (3H, d, $J=6.4$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.78 (3H, d, $J=6.4$ Hz, $\text{CH}(\text{CH}_3)_2$).

c) [4-(N-Hydroxyamino)-2R-isobutyl-succinyl]-L-3-methyl-4-methoxy-phenylalanine-N-methylamide

[4-(N-Benzyloxyamino)-2R-isobutyl-succinyl]-L-3-methyl-4-methoxy-phenylalanine-N-methylamide (70 mg, 0.14 mmol) was hydrogenated as described in example 10c to give the hydroxamic acid (40 mg, 0.1 mmol, 71%): m.p. $170 - 171^{\circ}$: $^1\text{H-NMR}$; δ (Methanol- d_4), 10.44 (1H, s, CONHOH), 8.81 (1H, s, CONHOH), 8.00 (1H, bd, CONHCH), 7.88 (1H, bm, CONHMe), 6.97 (2H, m, Aryl-H), 6.79 (1H, d, $J=8.9$ Hz, Aryl-H), 4.31 (1H, m, NHCHCO), 3.75 (3H,

s, OCH_3), 2.94 (1H, m, CH_2Ar), 2.78 - 2.43 (5H, bm, CONHCH_3 , CH_2Ar and $\text{CH}_2\text{CO}_2^t\text{Bu}$), 2.13 (3H, s, Aryl-CH_3), 2.13 - 1.88 (2H, m, $\text{CH}_2\text{CO}_2^t\text{Bu}$ and $^t\text{BuCH}$), 1.25 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.97 (1H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.78 (3H, d, $J=6.4$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.72 (3H, d, $J=6.4$ Hz, $\text{CH}(\text{CH}_3)_2$)

1 CLAIMS

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3 1. A compound of general formula I

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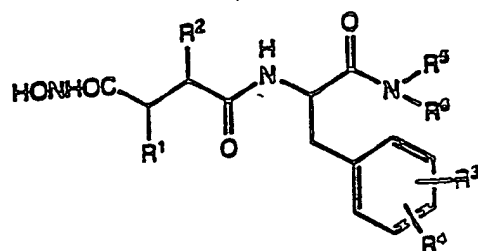
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33



I

Wherein :

R^1 is hydrogen, $C_1 - C_6$ alkyl, phenyl, substituted phenyl, phenyl($C_1 - C_6$ alkyl), or heterocyclyl;

or R^1 is ASO_nR^7

wherein A represents a $C_1 - C_6$ hydrocarbon chain, optionally substituted with one or more $C_1 - C_6$ alkyl, phenyl or substituted phenyl groups

$n = 0, 1, 2;$

R^7 is $C_1 - C_6$ alkyl, phenyl, substituted phenyl, phenyl ($C_1 - C_6$ alkyl), heterocyclyl, ($C_1 - C_6$ alkyl)acyl, thienyl or phenacyl;

R^2 is hydrogen, $C_1 - C_6$ alkyl, $C_2 - C_6$ alkenyl, phenyl ($C_1 - C_6$ alkyl) or cycloalkyl($C_1 - C_6$ alkyl);

R^3 and R^4 are selected from hydrogen, halogen, cyano

1 amino, amino(C₁ - C₆)alkyl, amino di(C₁ - C₆)alkyl,
2 amino(C₁ - C₆)alkylacyl, aminophenacyl, amino
3 (substituted) phenacyl, amino acid or derivative
4 thereof, hydroxy, oxy(C₁ - C₆)alkyl, oxyacyl, formyl,
5 carboxylic acid, carboxamide, carboxy(C₁ - C₆)
6 alkylamide, carboxyphenylamide, carboxy(C₁ - C₆) alkyl,
7 hydroxy(C₁ - C₆)alkyl, (C₁ - C₆)alkyloxy(C₁ - C₆) alkyl
8 or acyloxy(C₁ - C₆)alkyl, (C₁ - C₆)alkylcarboxylic
9 acid, (C₁-C₆) alkylcarboxy(C₁ - C₆) alkyl, amino
10 (C₁-C₆)alkylacyl carboxylic acid or amino
11 (C₁-C₆)alkylacyl (C₁-C₆) alkylcarboxylate;
12
13 or R³ is OCH₂COR⁸ and R⁴ is hydrogen;
14
15 wherein R⁸ is hydroxyl, C₁ - C₆ oxyalkyl, C₁ - C₆
16 oxyalkylphenyl, amino, C₁ - C₆ aminoalkyl, C₁ - C₆
17 aminodialkyl, C₁ - C₆ aminoalkylphenyl, an amino acid
18 or derivative thereof;
19
20 or R³ is OCH₂CH₂OR⁹ and R⁴ is hydrogen;
21
22 wherein R⁹ is C₁ - C₆ alkyl, C₁ - C₆ alkylphenyl,
23 phenyl, substituted phenyl, (C₁ - C₆ alkyl)acyl, or
24 phenacyl;
25
26 or R³ is OCH₂CN and R⁴ is hydrogen;
27
28 R⁵ is hydrogen or C₁ - C₆ alkyl, or (C₁ - C₆)
29 alkylphenyl;
30
31 R⁶ is hydrogen or methyl;
32 or a salt thereof;
33

1 specifically excluded are compounds wherein:

2

3 $R^3 = R^4 = \text{hydrogen}$

4

5 or $R^3 = R^4 = \text{hydroxy}$

6

7 or $R^3 = \text{hydrogen}$ and $R^4 = \text{oxybenzyl}$

8 or $R^3 = \text{hydrogen}$ and $R^4 = \text{oxy}(C_1 - C_6 \text{ alkyl})$;

9

10 or a salt thereof.

11

12 2. A compound as claimed in Claim 1, in which the
13 chiral centre adjacent to the substituent R^2 has R
14 stereochemistry.

15

16 3. A compound as claimed in Claim 1, in which the
17 chiral centre adjacent to the substituted benzyl group
18 has S stereochemistry.

19

20 4. A compound as claimed in Claim 1, in which the
21 chiral centre adjacent to R^1 has S stereochemistry.

22

23 5. A compound as claimed in Claim 1 in which R^1
24 represents a hydrogen atom or a $C_1 - C_4$ alkyl group,
25 or an arylthiomethyl group or a thiophenethiomethyl
26 group.

27

28 6. A compound as claimed in Claim 1 in which R^2
29 represents a $C_3 - C_6$ alkyl group.

30

31 7. A compound as claimed in Claim 1 in which R^3
32 represents cyano, aminoalkylacyl, amino
33 (C_{1-6}) alkylacylcarboxylic acid, amino (C_{1-6}) alkylacyl

1 (C₁₋₆)alkylcarboxylate or OCH₂COR⁸ and R⁴ is hydrogen;
2

3 Wherein R⁸ is as defined above.
4

5 8. A compound as claimed in Claim 1 in which R⁵
6 represents a C₁₋₅ alkyl group.
7

8 9. A compound as claimed in Claim 1 in which R⁶
9 represents a hydrogen atom.
10

11 10. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-
12 oxymethylcarboxylicacid) phenylalanine-N-methylamide;
13

14 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl
15 carboxy-N-methylamide)phenylalanine-N-methylamide;
16

17 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl
18 carboxy-beta-alanine)phenylalanine-N-methylamide;
19

20 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
21 (4-oxymethylcarboxyglycine)phenylalanine-N-methylamide;
22

23 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl
24 carboxy-N-benzylamide)phenylalanine-N-methylamide;
25

26 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-cyano)
27 phenylalanine-N-methylamide;
28

29 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-
30 acetamido)phenylalanine-N-methylamide;
31

32 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxy-
33 methylcarboxamide)-phenylalanine-N-methylamide;

- 1
- 2 [4-(N-hydroxyamino)-2R-isobutyl-3S-(2-thienylthio
- 3 methyl succinyl]-L-(4-N-acetylamino)-phenylalanine-N-
- 4 methylamide;
- 5
- 6 [4-(N-hydroxyamino)-2R-isobutyl-3S-(2-thienylthio-
- 7 methylsuccinyl]-L-(4-N-methylsuccinylamide)-phenyl-
- 8 alanine-N-methylamide;
- 9
- 10 [4-(N-hydroxyamino)-2R-isobutyl-3S-(4-aminophenylthio-
- 11 methyl)-succinyl]-L-(4-N-(methylsuccinylamide)-phenyl-
- 12 alanine-N-methylamide;
- 13
- 14 [4-(N-hydroxyamino)-2R-isobutyl-3S-(4-aminophenylthio-
- 15 methyl)-succinyl]-L-(4-N-(4-(4-oxobutanoic
- 16 acid)-aminophenylalanine-N-methylamide;
- 17
- 18 [4-(N-hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenyl-
- 19 thiomethyl)-succinyl]-L-(4-N-(methylsuccinylamido)-
- 20 phenylalanine-N-methylamide;
- 21
- 22 [4-(N(hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenyl-
- 23 thiomethyl)-succinyl]-L-(4-N-(4-(4-oxobutanoic
- 24 acid)-aminophenylalanine-N-methylamide;
- 25
- 26 [4-(N-hydroxyamino)-2R-isobutyl-3S-(2-thienylthio-
- 27 methyl)-succinyl]-L-4-(oxymethylcarboxymethyl)-phenyl-
- 28 alanine-N-methylamide;
- 29
- 30 [4-(N-hydroxyamino)-2R-isobutyl-3S-(2-thienylthio-
- 31 methyl)-succinyl]-L-(4-N-(oxymethylcarboxylic
- 32 acid)-phenylalanine-N-methylamide;
- 33

1 [4-(N-hydroxyamino)-2R-isobutyl-3S-(2-thienylthio-
2 methyl)-succinyl]-L-4-(oxymethylcarboxyglycyl methyl
3 ester)-phenylalanine-N-methylamide;

4
5 [4-(N-hydroxyamino)-2R-isobutyl-3S-(2-thienylthio-
6 methyl)-succinyl]-L-4-(oxymethylcarboxyglycine)-
7 phenylalanine-N-methylamide;

8
9 [4-(N-hydroxyamino)-2R-isobutyl-3S-methyl-succinyl]-L-
10 4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-
11 N-methylamide;

12 [4-(N-hydroxyamino)-2R-isobutyl-(3S-methyl-succinyl)-L-
13 4-(oxymethylcarboxyglycine)-phenylalanine-N-methyl-
14 amide;

15
16 [4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-4-(oxy-
17 methyl nitrile)-phenylalanine-N-methylamide;

18
19 [4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-3-(1-(2-
20 methoxycarbonyl)-ethyl)-4-methoxyphenylalanine-N-
21 methylamide;

22
23 [4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-3-(hydroxy-
24 methyl)-4-methoxyphenylalanine-N-methylamide; or

25
26 [4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-3-methyl-4-
27 methoxyphenylalanine-N-methylamide.

28
29 or a salt of one of them.

30
31 11. A compound as claimed in Claim 1 for use in human
32 or veterinary medicine.

33

1 12. The use of a compound as claimed in Claim 1 in
2 the preparation of an agent for use in the management
3 of disease involving collagen breakdown.

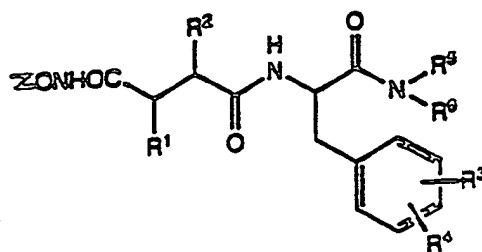
4
5 13. A pharmaceutical or veterinary composition
6 comprising a compound as claimed in Claim 1 together
7 with a pharmaceutically and/or veterinarily acceptable
8 carrier.

9
10 14. A composition as claimed in Claim 13 in unit
11 dosage form and comprising 10-500mg of a compound of
12 formula I.

13
14 15. A method for the treatment or prophylaxis of
15 disease involving collagen breakdown, the method
16 comprising administering to a patient an effective
17 amount of a compound as claimed in claim 1.

18
19 16. A process for the preparation of a compound of
20 formula I comprising:

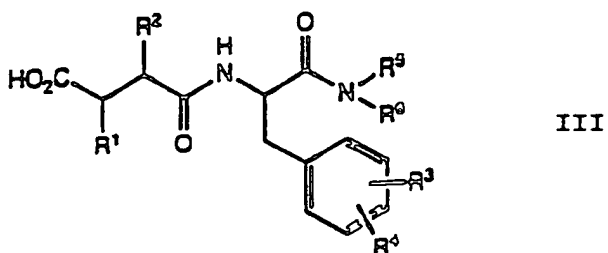
21
22 a) deprotection of a compound of formula II,



33 wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as defined for

1 general formula I and Z represents a protective group;
 2 or

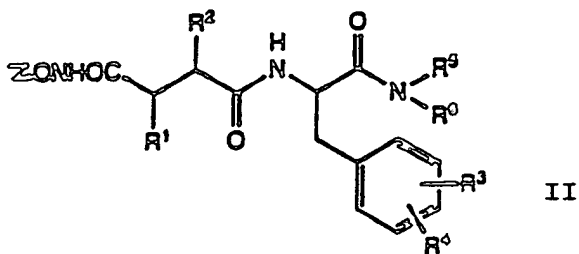
3
 4 b) reacting a compound of formula III:



13 wherein: R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as defined for
 14 general formula I, with hydroxylamine or a salt
 15 thereof; and

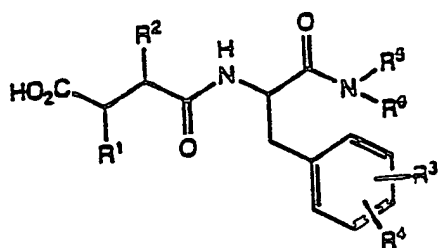
16
 17 c) optionally after step (a) or step (b) converting a
 18 compound of general formula I into another compound of
 19 general formula I.

20
 21 17. A compound of general formula II,



32 wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as defined for
 33 general formula I and Z is a protective group.

18. A compound of general formula III,



III

wherein R¹, R², R³, R⁴, R⁵ and R⁶ are as defined for
general formula I

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PCT/GB 92/00230

Form PCT/ISA/210 (10-2012) (English)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
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ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. GB 9200230
SA 56204

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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